US 20230076643A1

(19) **United States**

(12) **Patent Application Publication** (10) **Pub. No.: US 2023/0076643 A1**

Casimiro et al. (43) **Pub. Date: Mar. 9, 2023**

(54) **METHODS OF MAKING AND USING REGULATORY T CELLS AND EFFECTOR T CELLS HAVING CHIMERIC ANTIGEN RECEPTORS TARGETED TO CD6, CD19, AND/OR AN IL-13R FOR TREATMENT OF AUTOIMMUNE DISORDERS AND CANCERS**

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(21) Appl. No.: **17/789,930**

(22) PCT Filed: **Dec. 30, 2020**

(86) PCT No.: **PCT/US2020/067519**

§ 371 (c)(1),
(2) Date: **Jun. 29, 2022**

Related U.S. Application Data

(60) Provisional application No. 62/955,389, filed on Dec. 30, 2019.

Publication Classification

(51) **Int. Cl.**

C07K 16/28	(2006.01)
C12N 15/86	(2006.01)
A61K 35/17	(2006.01)
C07K 16/24	(2006.01)
A61P 35/00	(2006.01)

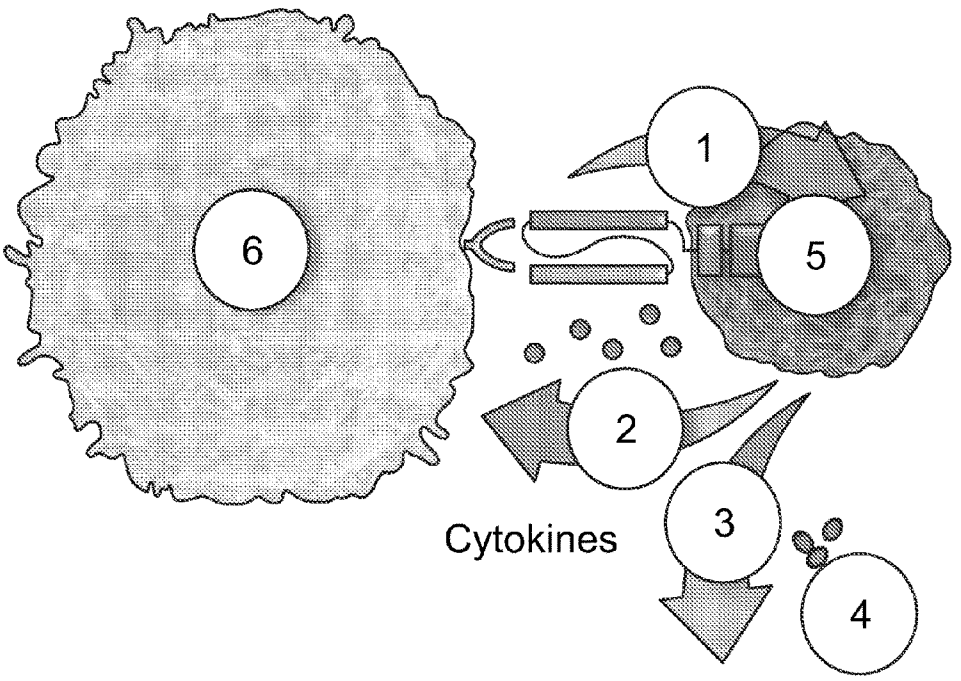
(52) **U.S. Cl.**

CPC ***C07K 16/2896*** (2013.01); ***C12N 15/86*** (2013.01); ***A61K 35/17*** (2013.01); ***C07K 16/244*** (2013.01); ***A61P 35/00*** (2018.01)

(57) **ABSTRACT**

Provided herein are, inter alia, CAR-T cell compositions targeting CD6, CD19, and/or an IL-13R, and methods useful for treating autoimmune diseases and cancer.

Specification includes a Sequence Listing.



1. CAR transduced T cells produced a tuned activation signaling upon antigen-specific recognition
2. Blunted cytokine release
3. Less off target effects (reduction CRS)
4. Minimized local and systematic tissue damage
5. CAR T-cell life extension
6. Equal or increased anti-cancer efficiency

pF03496 - CD6scFvop(VH_VL)-IgG4(L235E,N297Q)op-CTLA4-Zetaop

MLLLVTSLLLCELPHPAFLLIPEVQLVESGGGLVKPGGSLKLSCAASGFKFSRYAMSWVRQAPGKRLEWVATISSGGSYIY

Signal Sequence CD6scFv(Vh-Vl)

YPDSVKGRFTISRDNVKNTLYLQMSSLRSEDTAMYYCARRDYDLDYFDSWGQGTLVTVSSGSTSGGGSGGGSGGGGS

SDIQMTQSPSSLSASVGDRVTITCKASRDIRSYLTWYQQKPGKAPKTLIYYATSLADGVPSRFSGSGSGQDYSLTISSLESD

DTATYYCLQHGESPFTFGSGTKLEIKRAESKYGPPCPPCPAPEFEGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSQEDP

IgG4op(L235E,N297Q)

EVQFNWYVDGVEVHNAKTKPREEQFQSTYRVVSVLTVLHQDWLNGKEYKCKVSNKGLPSSIEKTISKAKGQPREPQVY

TLPPSQEEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSRLTVDKSRWQEGNVFSCSV

MHEALHNHYTQKSLSLSLGKMALIVLGGVAGLLLFIGLGIFFAVSLSKMLKKRSPLTTGVYVKMPPTEPECEKQFQPYFIPI

CD4 TM CTLA-4

NGGGRVKFSRSADAPAYQQGQNQLYNELNLGRREEYDVLDKRRGRDPEMGGKPRRKNPQEGLYNELQKDKMAEAY

Link CD3ζ

SEIGMKGERRRGKGHDGLYQGLSTATKDTYDALHMQALPPR

FIG. 1

pF03497 - CD6scFvop(VL_VH)-IgG4(L235E,N297Q)op-CTLA4-Zetaop

MLLLVTSLLLCELPHPAFLLIPDIQMTQSPSSLSASVGDRVTITCKASRDIRSYLTWYQQKPGKAPKTLIYYATSLADGVPS

Signal Sequence CD6scFv(Vl-Vh)

RFSGSGSGQDYSLTISSLESDDTATYYCLQHGESPFTFGSGTKLEIKRAGSTSGGGSGGGSGGGGSSEVQLVESGGGLVK

PGGSLKLSCAASGFKFSRYAMSWVRQAPGKRLEWVATISSGGSYIYYPDSVKGRFTISRDNVKNTLYLQMSSLRSEDTA

MYYCARRDYDLDYFDSWGQGTLVTVSSESKYGPPCPPCPAPEFEGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSQED

IgG4(L235E,N297Q)op

PEVQFNWYVDGVEVHNAKTKPREEQFQSTYRVVSVLTVLHQDWLNGKEYKCKVSNKGLPSSIEKTISKAKGQPREPQV

YTLPPSQEEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSRLTVDKSRWQEGNVFSCSV

MHEALHNHYTQKSLSLSLGKMALIVLGGVAGLLLFIGLGIFFAVSLSKMLKKRSPLTTGVYVKMPPTEPECEKQFQPYFIPI

CD4 TM CTLA-4

NGGGRVKFSRSADAPAYQQGQNQLYNELNLGRREEYDVLDKRRGRDPEMGGKPRRKNPQEGLYNELQKDKMAEAY

Link CD3ζ

SEIGMKGERRRGKGHDGLYQGLSTATKDTYDALHMQALPPR

FIG. 2

pF03488 - CD6scFv(VH-VL)-IgG4op(L235E, N297Q)-41BB-Zetaop

MLLLVTSLLLCELPHPAFLLIPEVQLVESGGGLVKPGGSLKLSCAASGFKFSRYAMSWVRQAPGKRLEWVATISSGGSYIY

Signal Sequence CD6scFv(Vh-Vl)

YPDSVKGRFTISRDNVKNTLYLQMSSLRSEDTAMYYCARRDYDLDYFDSWGQGTLVTVSSGSTSGGGSGGGSGGGGS

SDIQMTQSPSSLSASVGDRVTITCKASRDIRSYLTWYQQKPGKAPKTLIYYATSLADGVPSRFSGSGSGQDYSLTISSLESD

DTATYYCLQHGESPFTFGSGTKLEIKRAESKYGPPCPPCPAPEFEGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSQEDP

IgG4op(L235E, N297Q)

EVQFNWYVDGVEVHNAKTKPREEQFQSTYRVVSVLTVLHQDWLNGKEYKCKVSNKGLPSSIEKTISKAKGQPREPQVY

TLPPSQEEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSRLTVDKSRWQEGNVFSCSV

MHEALHNHYTQKSLSLSLGKMALIVLGGVAGLLLFIGLGIFFKRGRKKLLYIFKQPFMRPVQTTQEEDGCSCRFPEEEEGG

CD4 TM 41BB

CELGGGRVKFSRSADAPAYQQGQNQLYNELNLGRREEYDVLDKRRGRDPEMGGKPRRKNPQEGLYNELQKDKMAEA

Link CD3ζ

YSEIGMKGERRRGKGHDGLYQGLSTATKDTYDALHMQALPPR

FIG. 3

pF03491 - CD6scFv(VL-VH)-IgG4op(L235E, N297Q)-41BB-Zetaop

MLLLVTSLLLCELPHPAFLLIPDIQMTQSPSSLSASVGDRVTITCKASRDIRSYLTWYQQKPGKAPKTLIYYATSLADGVPS

Signal Sequence CD6scFv(Vl-Vh)

RFSGSGSGQDYSLTISSLESDDTATYYCLQHGESPFTFGSGTKLEIKRAGSTSGGGSGGGSGGGGSSEVQLVESGGGLVK

PGGSLKLSCAASGFKFSRYAMSWVRQAPGKRLEWVATISSGGSYIYYPDSVKGRFTISRDNVKNTLYLQMSSLRSEDTA

MYYCARRDYDLDYFDSWGQGTLVTVSSESKYGPPCPPCPAPEFEGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSQED

IgG4op(L235E, N297Q)

PEVQFNWYVDGVEVHNAKTKPREEQFQSTYRVVSVLTVLHQDWLNGKEYKCKVSNKGLPSSIEKTISKAKGQPREPQV

YTLPPSQEEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSRLTVDKSRWQEGNVFSCSV

MHEALHNHYTQKSLSLSLGKMALIVLGGVAGLLLFIGLGIFFKRGRKKLLYIFKQPFMRPVQTTQEEDGCSCRFPEEEEGG

CD4 TM 41BB

CELGGGRVKFSRSADAPAYQQGQNQLYNELNLGRREEYDVLDKRRGRDPEMGGKPRRKNPQEGLYNELQKDKMAEA

Link CD3ζ

YSEIGMKGERRRGKGHDGLYQGLSTATKDTYDALHMQALPPR

FIG. 4

EVQLVESGGGLVKPGGSLKLSCAASGFKFSRYAMSWVRQAPGKGLEWVATISSGGSYIYYPDSV

Heavy chain

KGRFTISRDNVKNTLYLQMSSLRSEDTAMYYCARRDYDLDYFDSWGQGTLVTVSSGSTSGGGSG

Linker

GGSGGGGSGDIQMTQSPSSLSASVGDRVTITCKASRDIRSYLTWYQQKPGKAPKTLIYYATSLA

Light chain

DGVPSRFSGSGSGQDYSLTISSLESDDTATYYCLQHGESPFTFGSGTKMEIK

(SEQ ID NO:73)

2H2 scFv (CD6 scFv mutant, from pF03496)

Mutations in bold + large font

FIG. 5

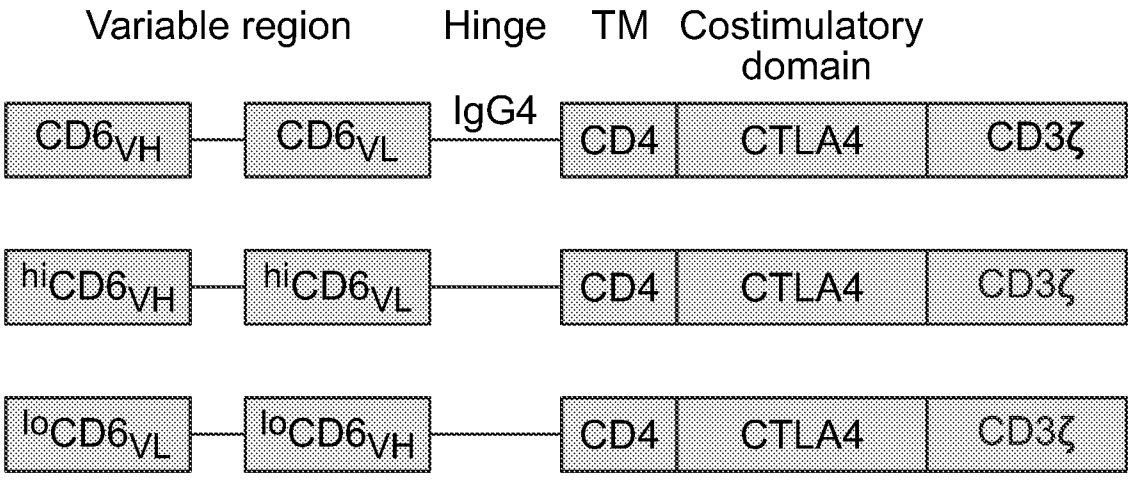

Variable region
Hinge
TM
Costimulatory domain
IgG4
$CD6_{VH}$
$CD6_{VL}$
CD4
CTLA4
CD3ζ
$^{hi}CD6_{VH}$
$^{hi}CD6_{VL}$
CD4
CTLA4
CD3ζ
$^{lo}CD6_{VL}$
$^{lo}CD6_{VH}$
CD4
CTLA4
CD3ζ

FIG. 6A

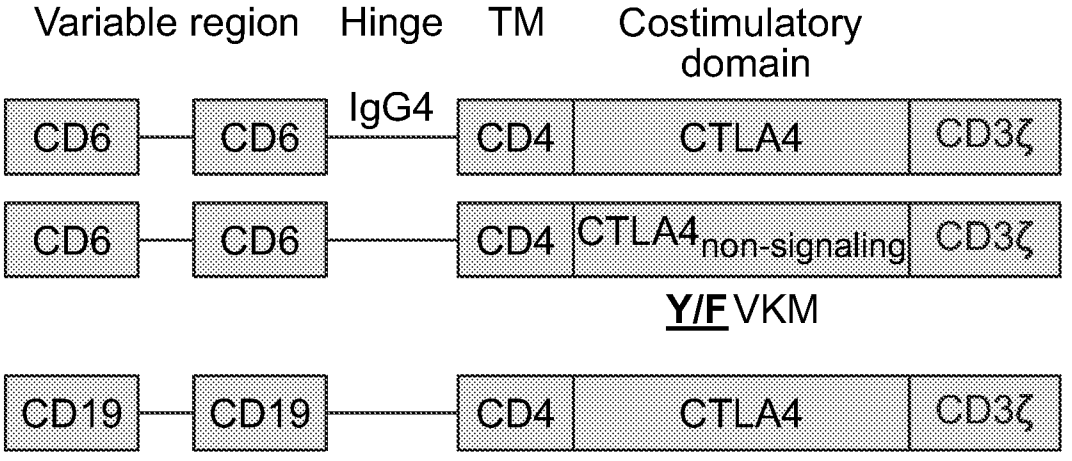
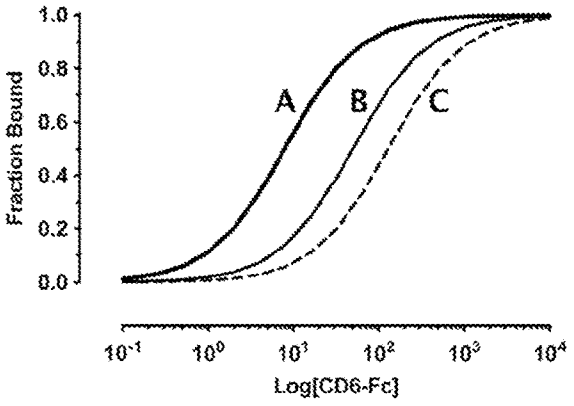

Variable region
Hinge
TM
Costimulatory domain
IgG4
CD6
CD6
CD4
CTLA4
CD3ζ
CD6
CD6
CD4
$CTLA4_{non\text{-}signaling}$
CD3ζ
Y/F VKM
CD19
CD19
CD4
CTLA4
CD3ζ

FIG. 6B



A: ^{hi}**VH-VL** (KD=7.9±2.0nM)
B: VH-VL (KD=50.0±2.9nM)
C: ^{lo}**VL-VH** (KD=129.5±12.1nM)

Substitutions in (B/A), the high affinity construct:
H_{44}FR2 (R/G)
$Linker_{18}$ (S/G)
L_{104}FR4 (L/M)

FIG. 7

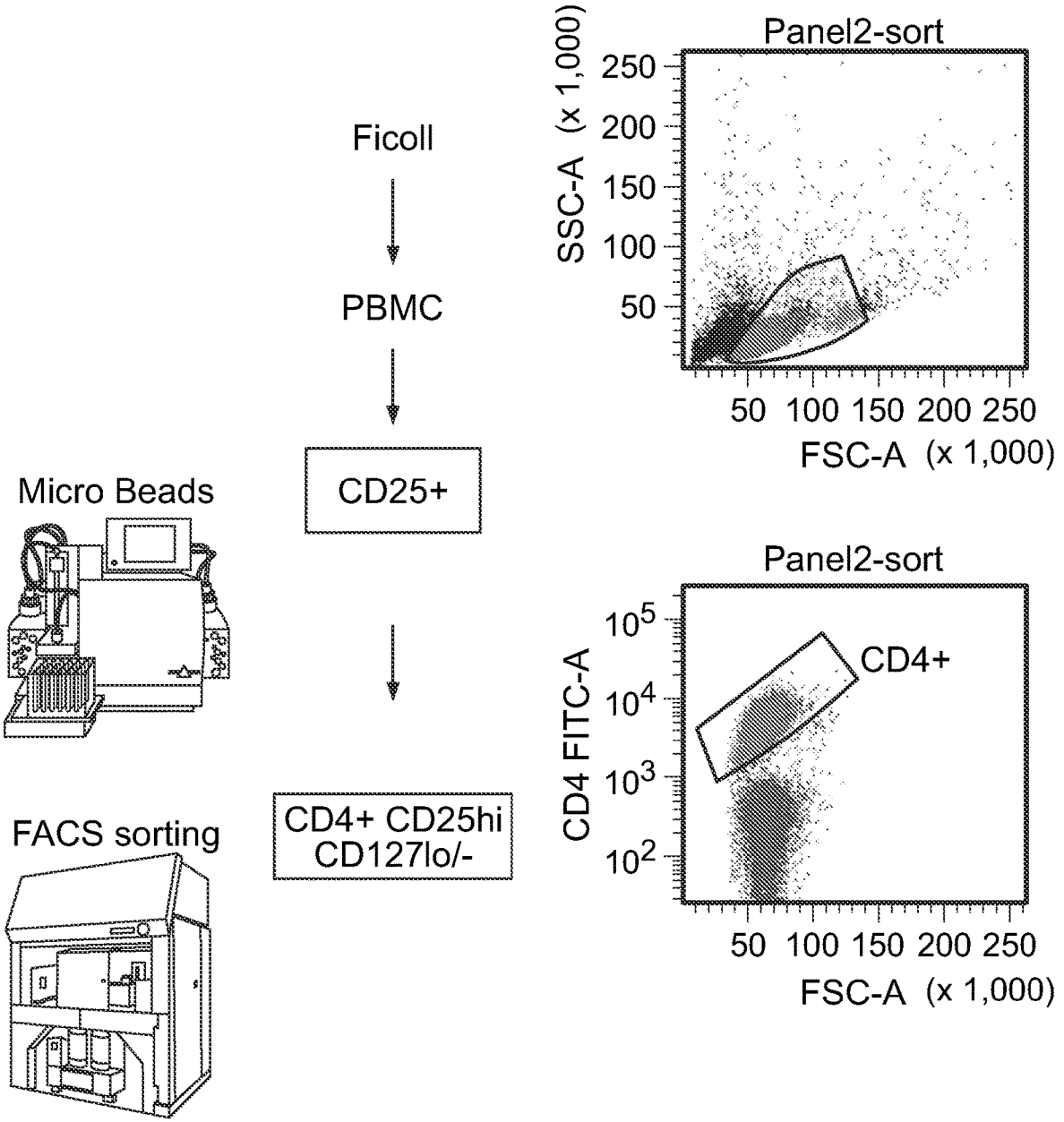
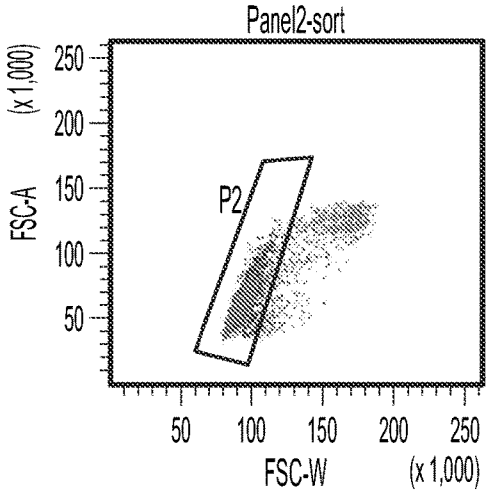
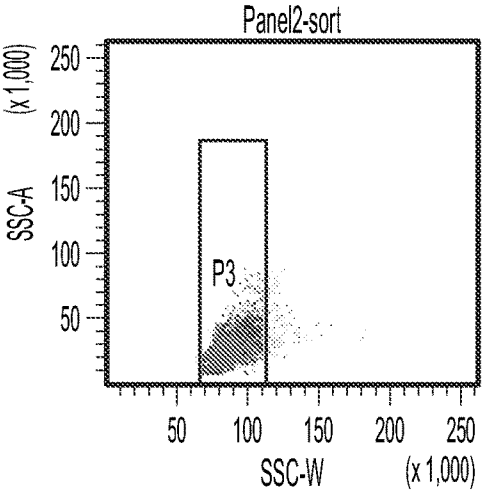
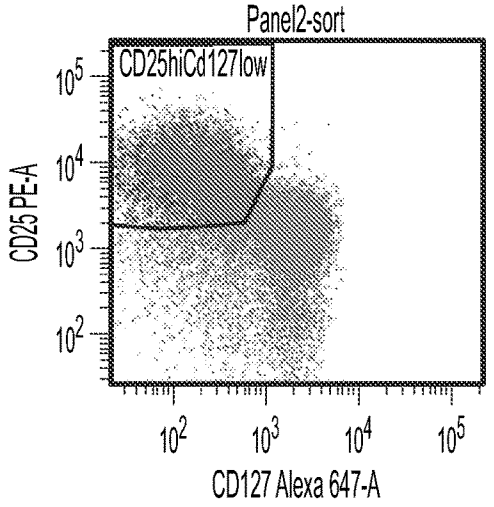

Ficoll
PBMC
CD25+
Micro Beads
CD4+ CD25hi
CD127lo/-
FACS sorting
Panel2-sort
SSC-A (x 1,000)
250
200
150
100
50
50 100 150 200 250
FSC-A (x 1,000)
Panel2-sort
CD4 FITC-A
10^5
10^4
10^3
10^2
CD4+
50 100 150 200 250
FSC-A (x 1,000)

FIG. 8







Tube: sort

Population	#Events	%Parent	%Total
All Events	50,000	####	100.0
P1	43,911	87.8	87.8
P2	43,303	98.6	86.6
P3	43,223	99.8	86.4
CD4+	24,305	56.2	48.6
CD25hiCd127low	12,812	52.7	25.6

70um
NIF
Chiller 4C
FR: 4
User chose sort regions

FIG. 8 (Cont.)

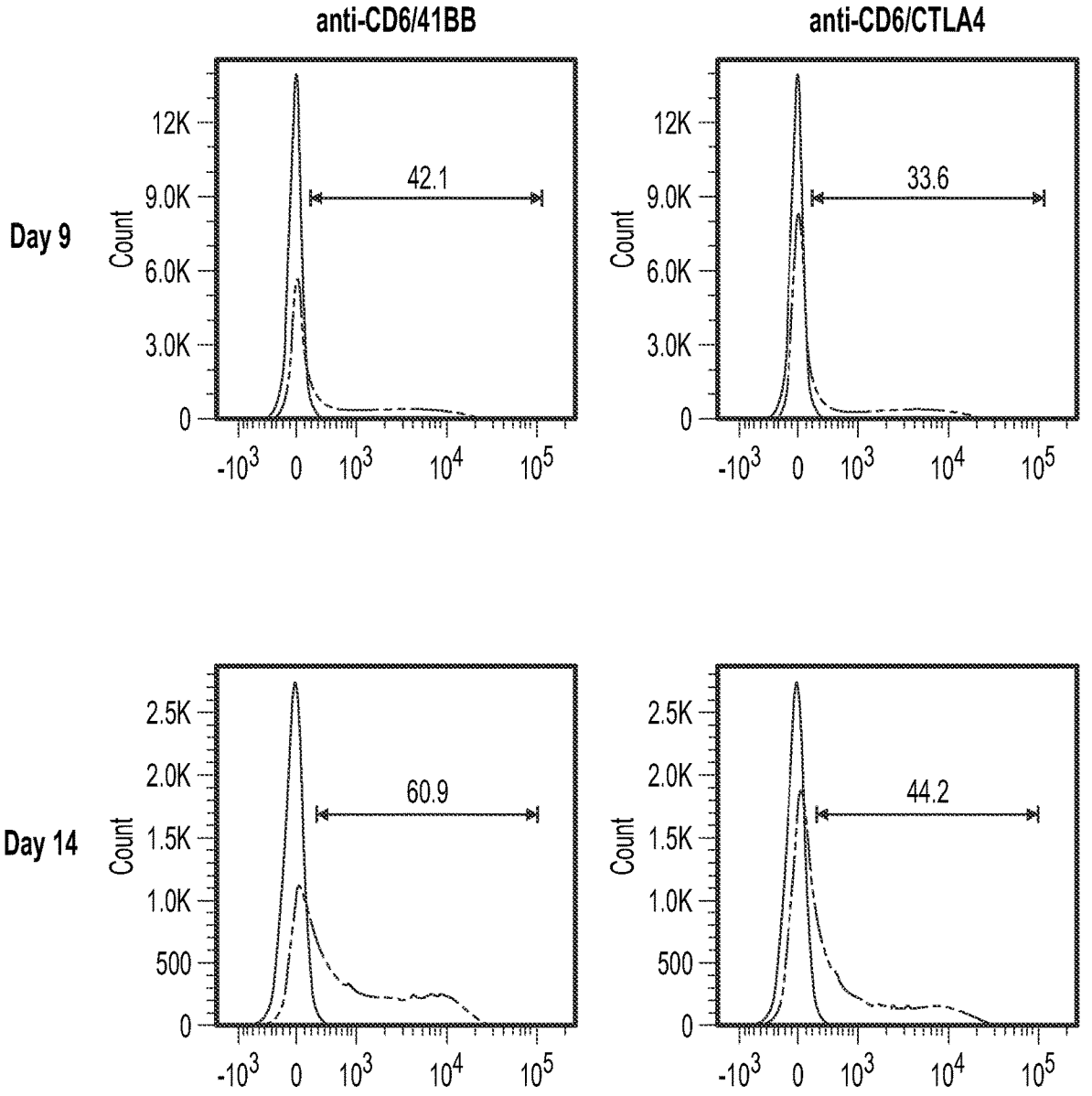

anti-CD6/41BB
anti-CD6/CTLA4
Day 9
Day 14
Count
12K
9.0K
6.0K
3.0K
0
2.5K
2.0K
1.5K
1.0K
500
42.1
33.6
60.9
44.2
-10^3
0
10^3
10^4
10^5

FIG. 9

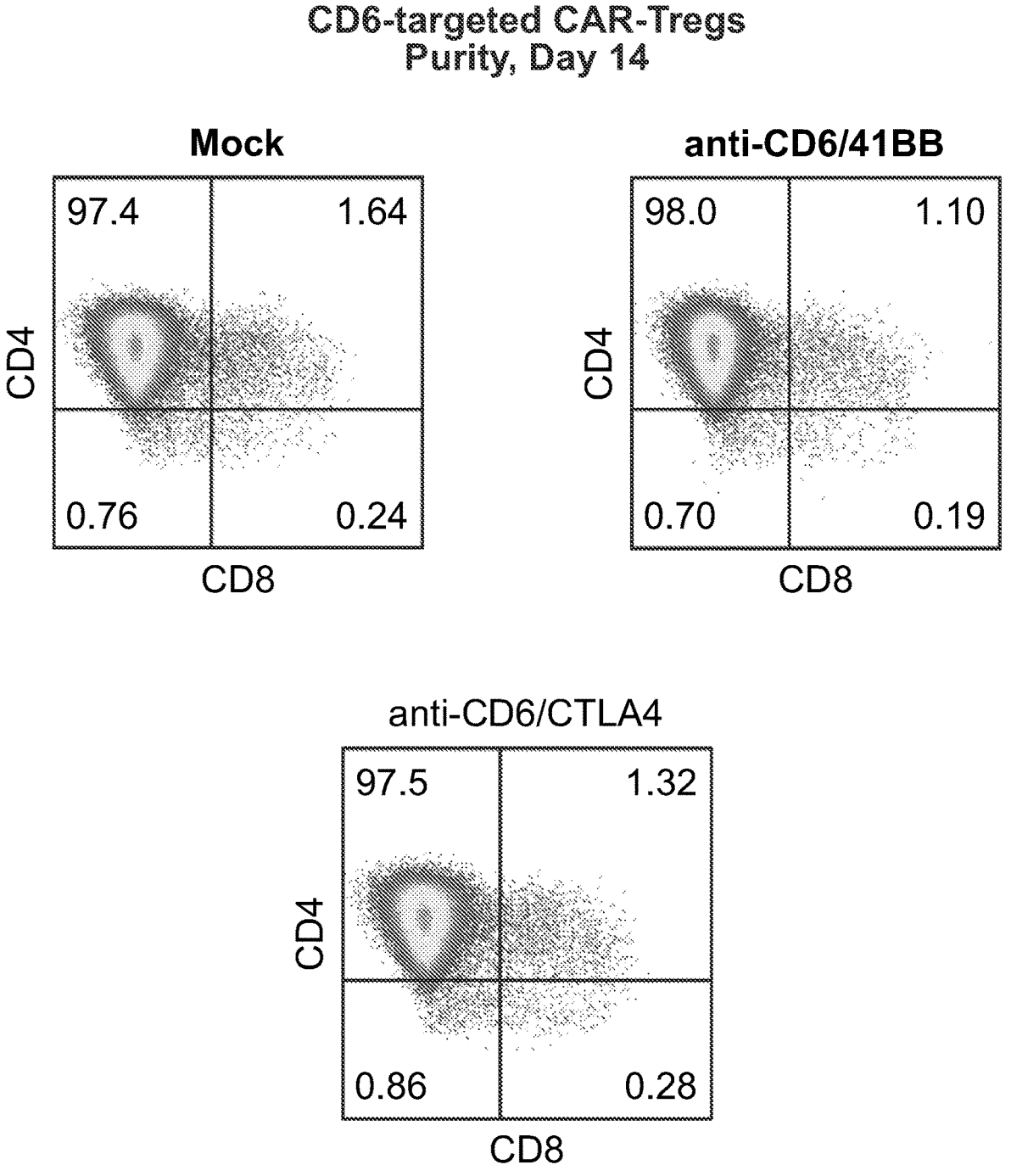

CD6-targeted CAR-Tregs
Purity, Day 14
Mock
97.4
1.64
0.76
0.24
CD4
CD8
anti-CD6/41BB
98.0
1.10
0.70
0.19
CD4
CD8
anti-CD6/CTLA4
97.5
1.32
0.86
0.28
CD4
CD8

FIG. 10

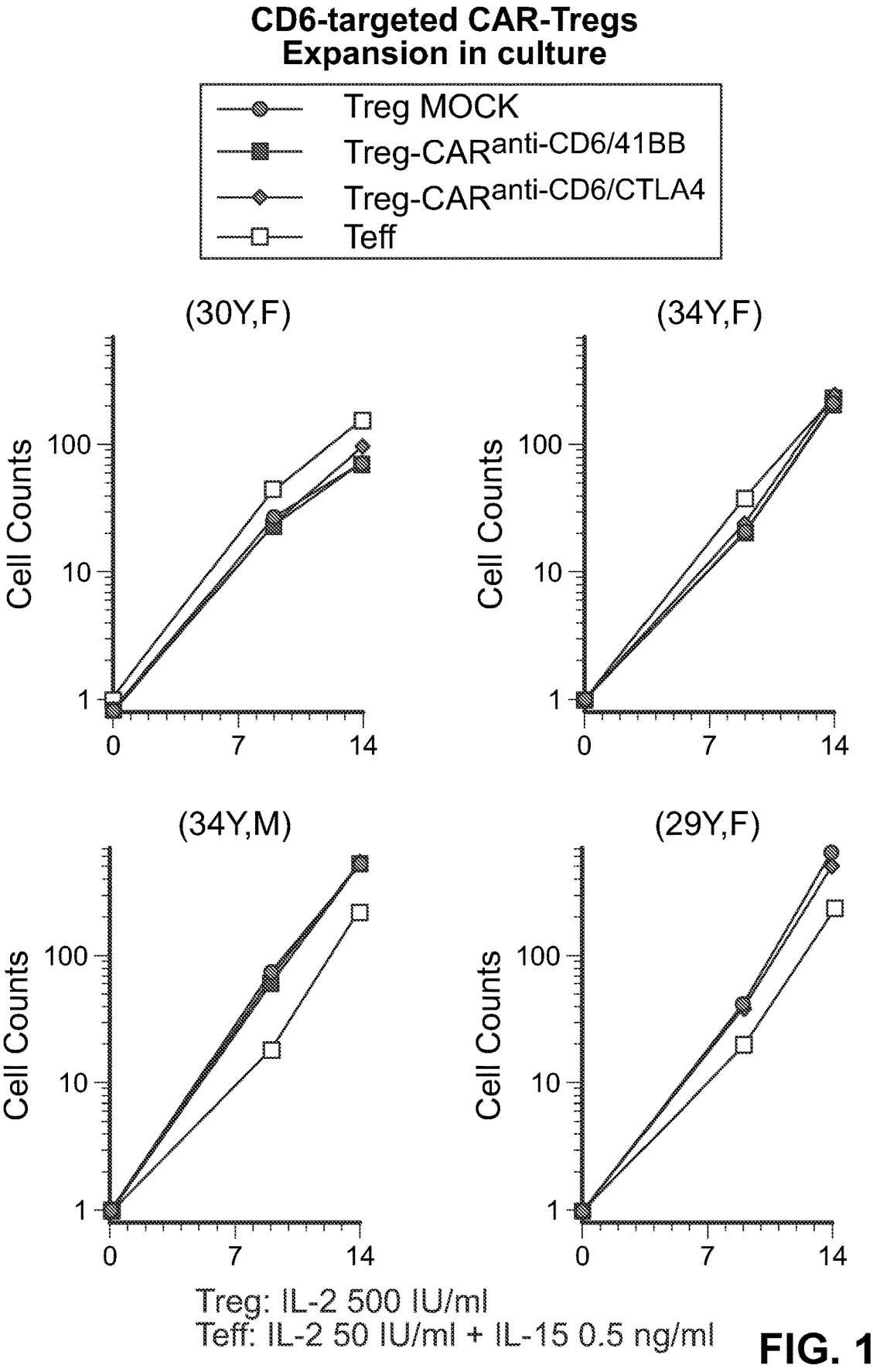

CD6-targeted CAR-Tregs
Expansion in culture
Treg MOCK
Treg-CARanti-CD6/41BB
Treg-CARanti-CD6/CTLA4
Teff
(30Y,F)
(34Y,F)
(34Y,M)
(29Y,F)
Cell Counts
100
10
1
0
7
14
Treg: IL-2 500 IU/ml
Teff: IL-2 50 IU/ml + IL-15 0.5 ng/ml

FIG. 11

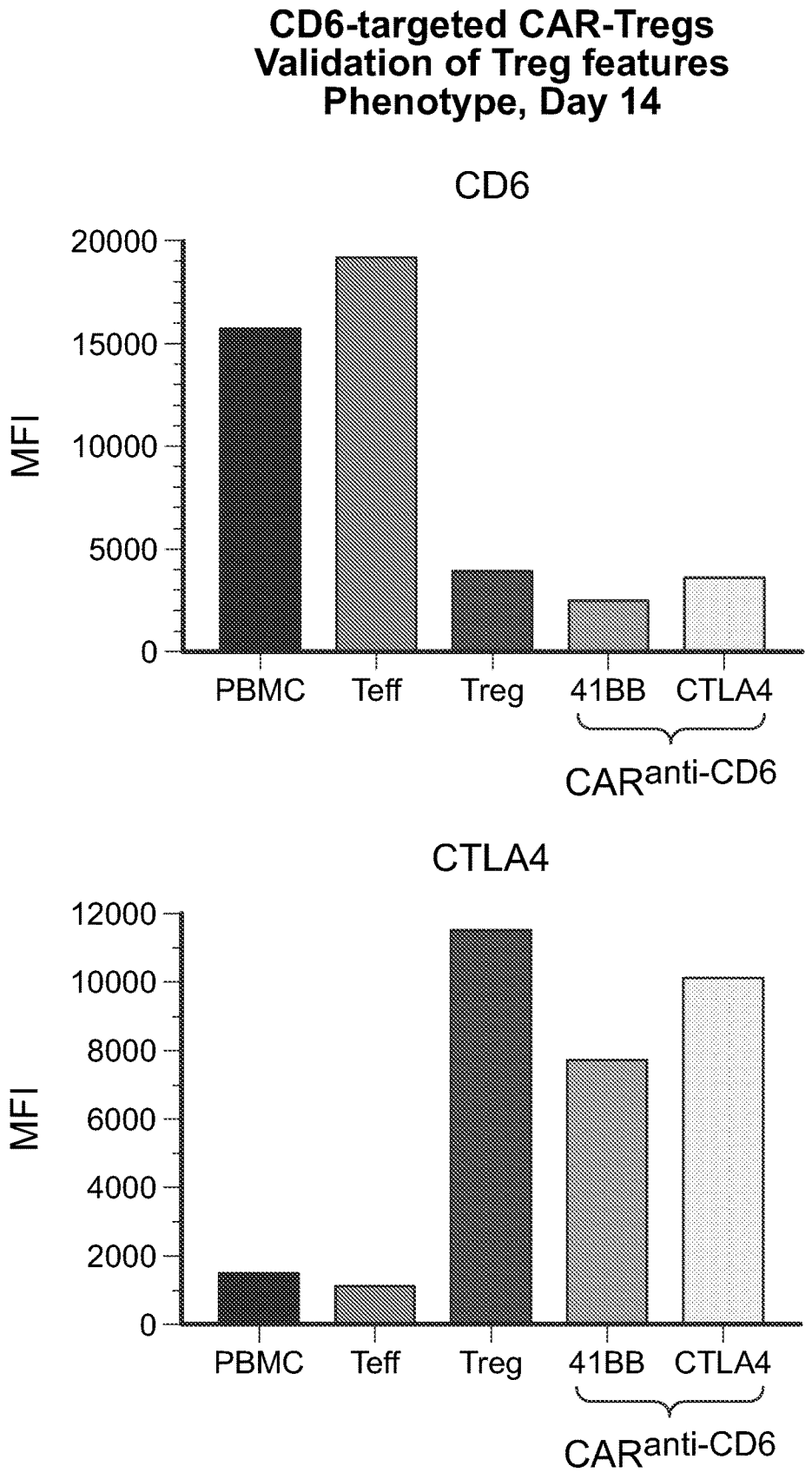
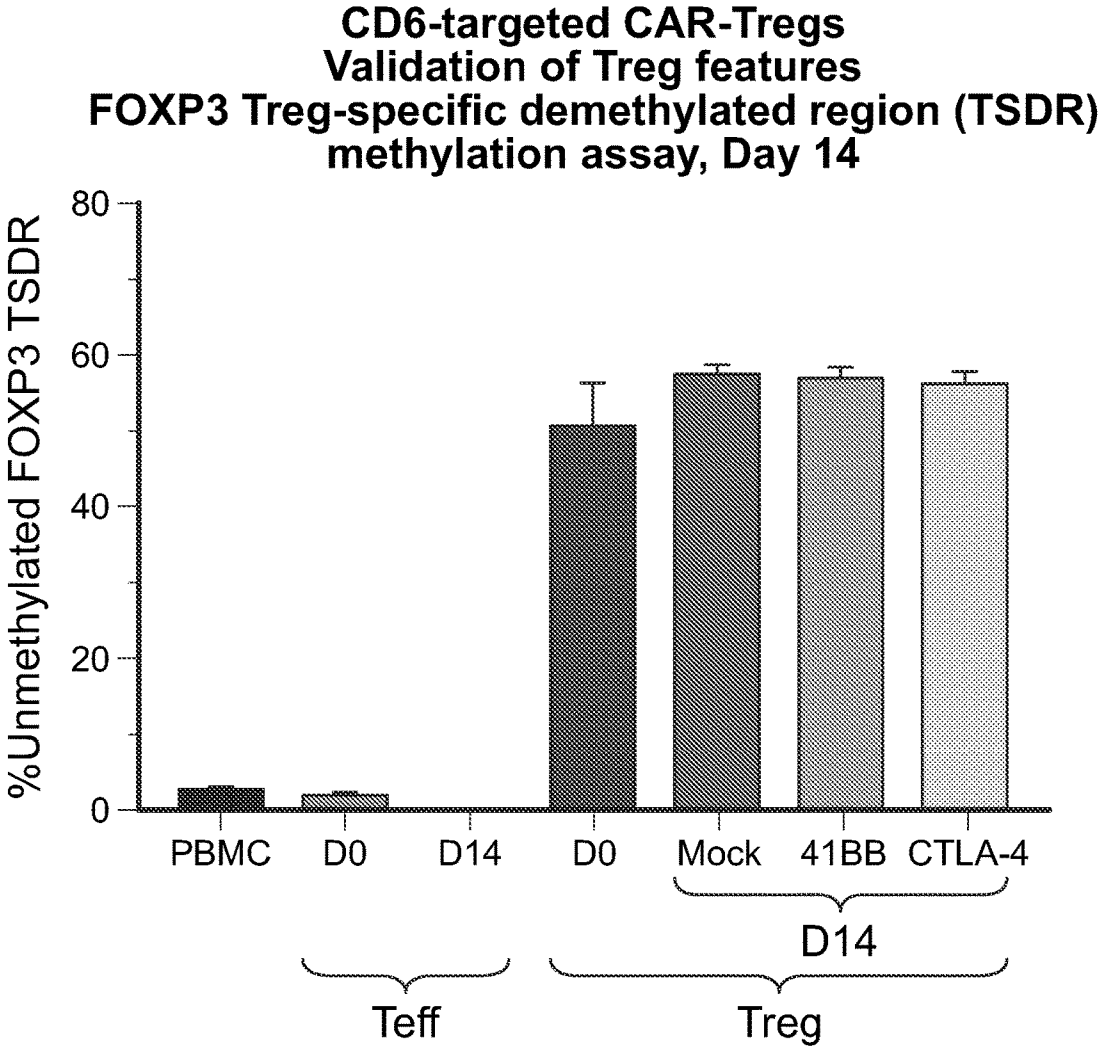

CD6-targeted CAR-Tregs
Validation of Treg features
Phenotype, Day 14
CD6
MFI
20000
15000
10000
5000
0
PBMC
Teff
Treg
41BB
CTLA4
CARanti-CD6
CTLA4
MFI
12000
10000
8000
6000
4000
2000
0
PBMC
Teff
Treg
41BB
CTLA4
CARanti-CD6

FIG. 12



Donor: 30, Female

Reference: For female Tregs, the percentages calculated are multiplied by 2 to correct for X-chromosome inactivation

Sci Transl Med. 2015:7(315):315ra189.

FIG. 13

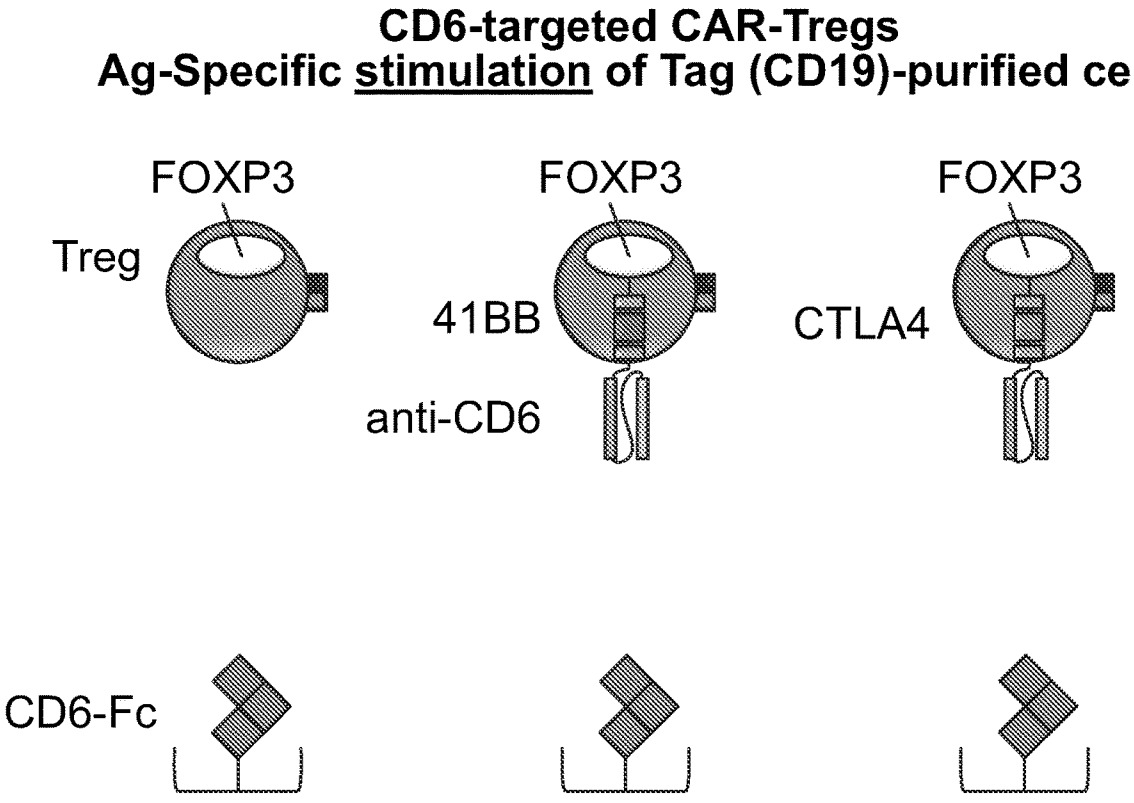

CD6-targeted CAR-Tregs
Ag-Specific stimulation of Tag (CD19)-purified cells
FOXP3
Treg
FOXP3
41BB
anti-CD6
FOXP3
CTLA4
CD6-Fc

FIG. 14A

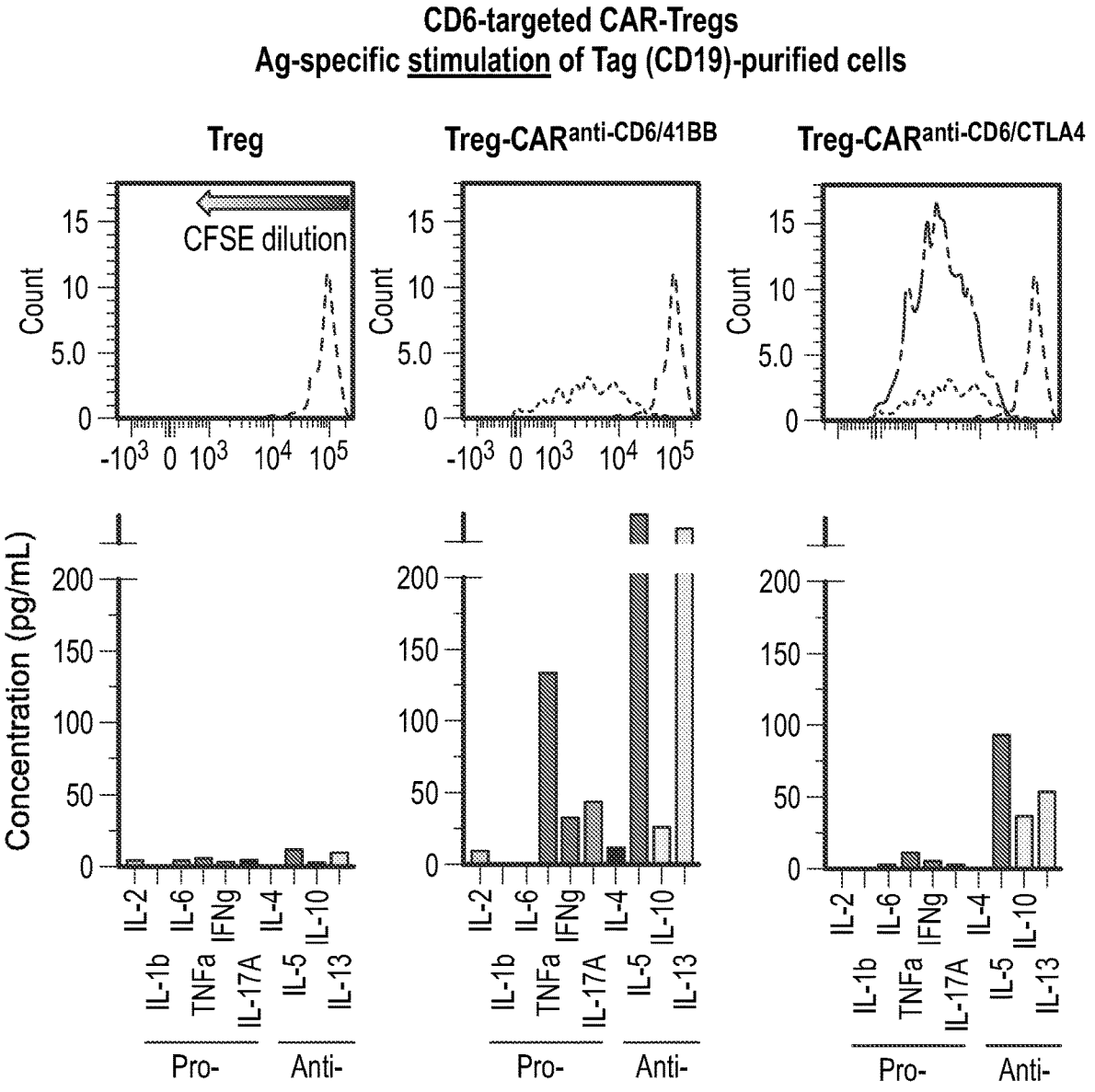

CD6-targeted CAR-Tregs
Ag-specific stimulation of Tag (CD19)-purified cells
Treg
Treg-CARanti-CD6/41BB
Treg-CARanti-CD6/CTLA4
CFSE dilution
Count
15
10
5.0
0
-10^3 0 10^3 10^4 10^5
Concentration (pg/mL)
200
150
100
50
0
IL-2
IL-6
IFNg
IL-4
IL-10
IL-1b
TNFa
IL-17A
IL-5
IL-13
Pro-
Anti-

FIG. 14B

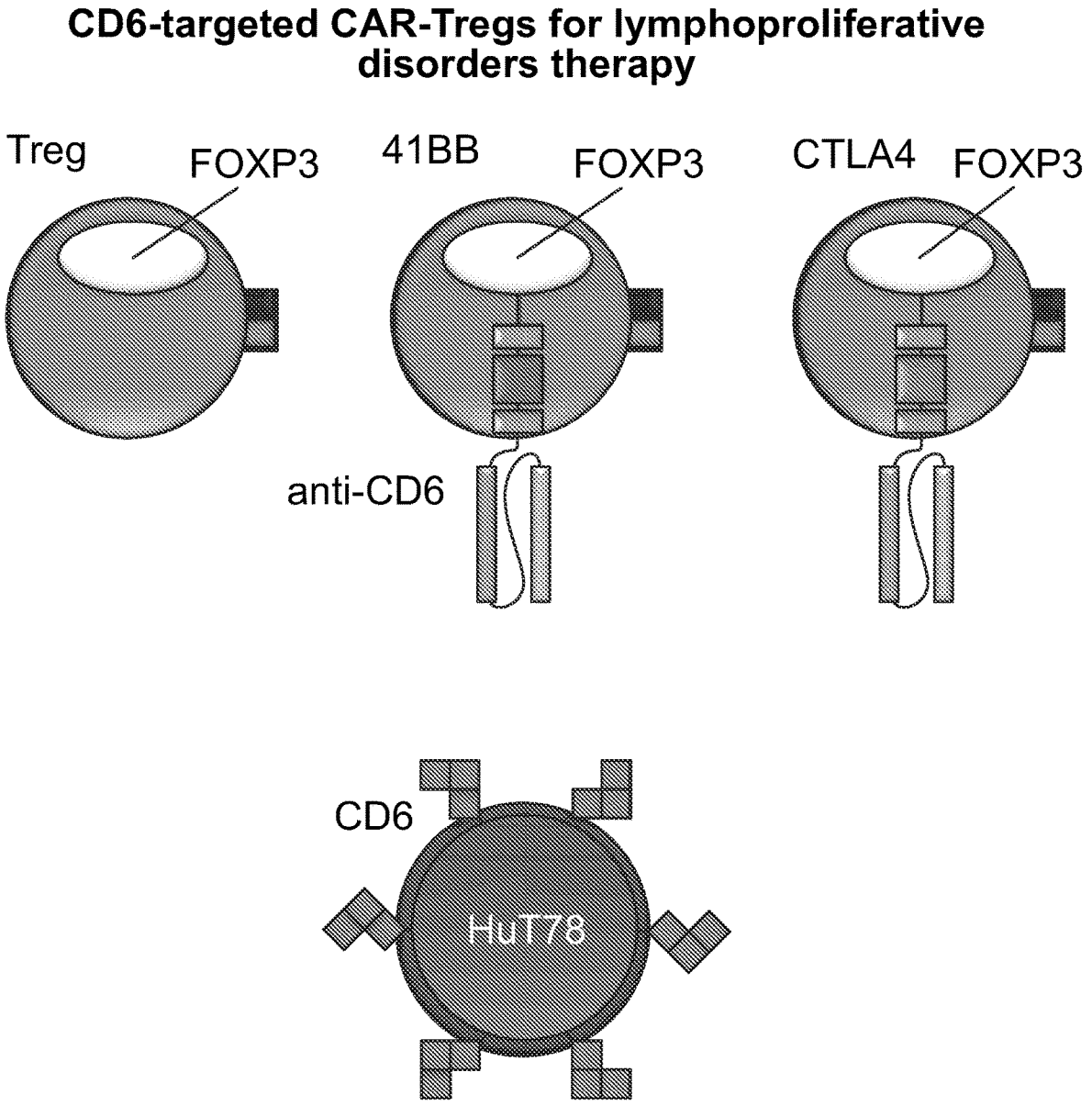
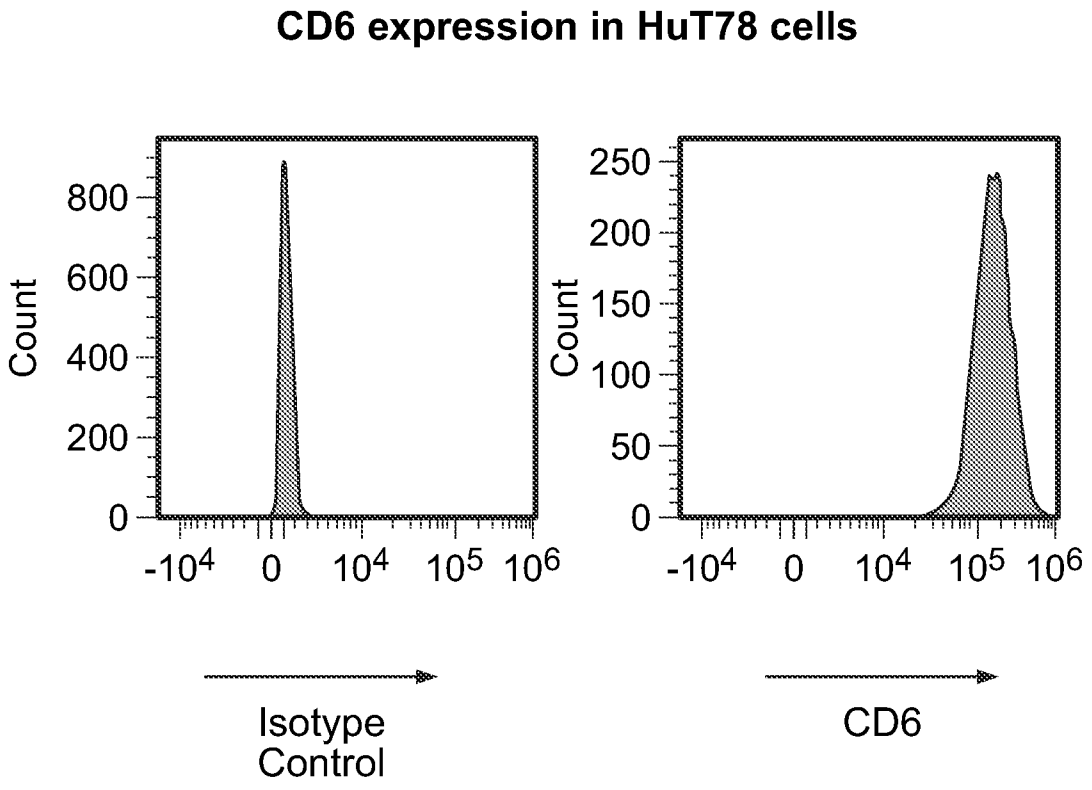

CD6-targeted CAR-Tregs for lymphoproliferative disorders therapy
Treg
FOXP3
41BB
FOXP3
CTLA4
FOXP3
anti-CD6
CD6
HuT78

FIG. 15A



HuT78 cell line: human cutaneous T lymphocyte from a Sezary Syndrome patient, male 53 y/o

FIG. 15B

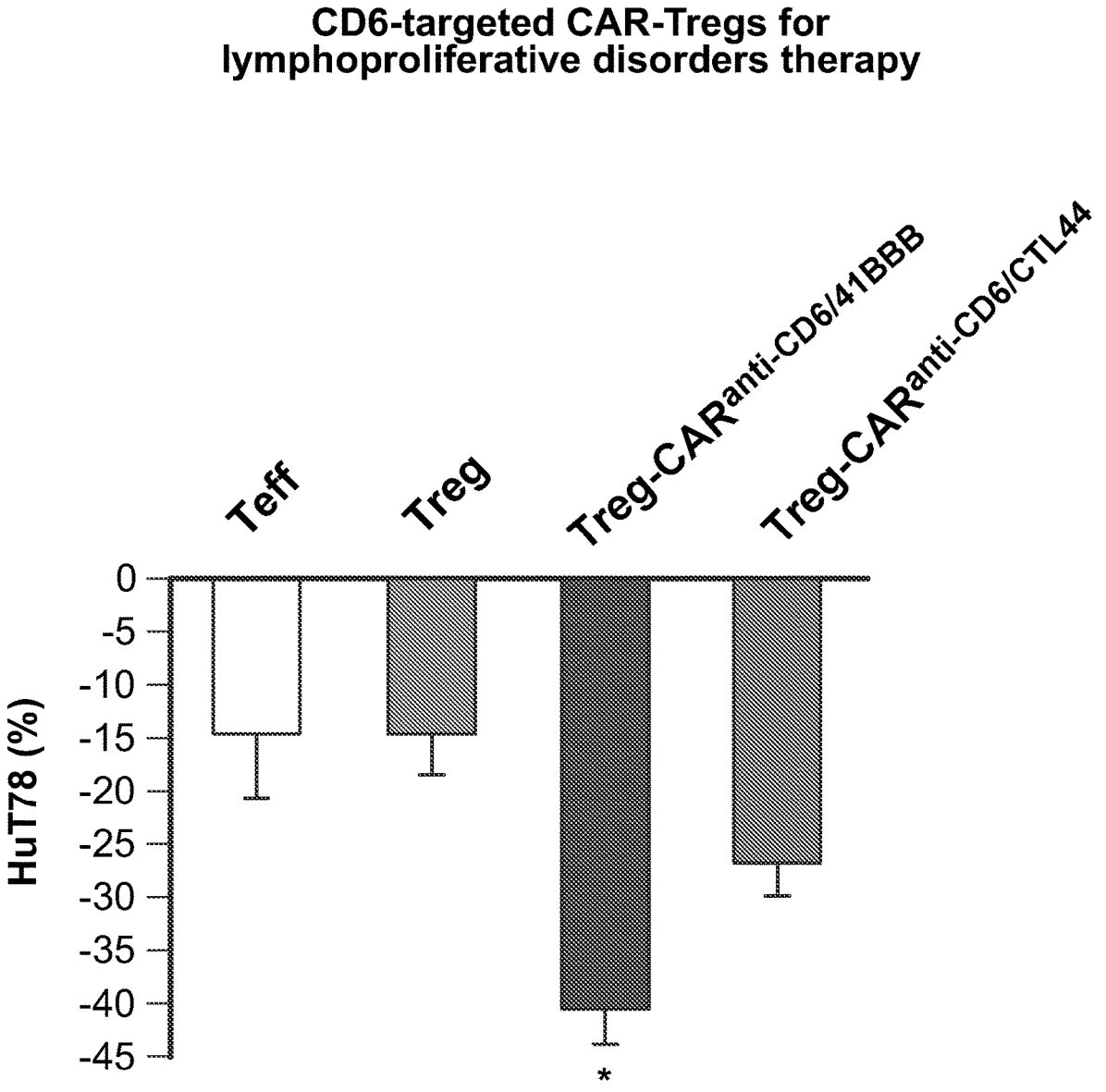

CD6-targeted CAR-Tregs for
lymphoproliferative disorders therapy
Teff
Treg
Treg-CARanti-CD6/41BBB
Treg-CARanti-CD6/CTL44
HuT78 (%)
0
-5
-10
-15
-20
-25
-30
-35
-40
-45
*

FIG. 15C

IL13op-IgG4op(L235E,N297Q)-CD4tmop-CTLA4-Zetaop-T2A-CD19t

MLLLVTSLLLCELPHPAFLLIPGPVPPSTALRYLIEELVNITQNQKAPLCNGSMVWSINLTAGM
YCAALESLINVSGCSAIEKTQRMLSGFCPHKVSAGQFSSLHVRDTKIEVAQFVKDLLLHLKKLF
REGRFNESKYGPPCPPCPAPEFEGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSQEDPEVQF
NWYVDGVEVHNAKTKPREEQFQSTYRVVSVLTVLHQDWLNGKEYKCKVSNKGLPSSIEKTIS
KAKGQPREPQVYTLPPSQEEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVL
DSDGSFFLYSRLTVDKSRWQEGNVFSCSVMHEALHNHYTQKSLSLSLGKMALIVLGGVAGLL
LFIGLGIFFAVSLSKMLKKRSPLTTGVYVKMPPTEPECEKQFQPYFIPINGGGRVKFSRSADAP
AYQQGQNQLYNELNLGRREEYDVLDKRRGRDPEMGGKPRRKNPQEGLYNELQKDKMAEA
YSEIGMKGERRRGKGHDGLYQGLSTATKDTYDALHMQALPPRLEGGGEGRGSLLTCGDVEE
NPGPRMPPPRLLFFLLFLTPMEVRPEEPLVVKVEEGDNAVLQCLKGTSDGPTQQLTWSRESP
LKPFLKLSLGLPGLGIHMRPLAIWLFIFNVSQQMGGFYLCQPGPPSEKAWQPGWTVNVEGS
GELFRWNVSDLGGLGCGLKNRSSEGPSSPSGKLMSPKLYVWAKDRPEIWEGEPPCVPPRDS
LNQSLSQDLTMAPGSTLWLSCGVPPDSVSRGPLSWTHVHPKGPKSLLSLELKDDRPARDM
WVMETGLLLPRATAQDAGKYYCHRGNLTMSFHLEITARPVLWHWLLRTGGWKVSAVTLA
YLIFCLCSLVGILHLQRALVLRRKR

GMCSFRa signal peptide
IL13
IgG4(L235E,N297Q)
CD4 transmembrane
CTLA4
(Gly)3
Zeta
T2A
CD19t

FIG. 16A

IL13op-IgG4op(L235E,N297Q)-CD4tmop-CTLA4-Zetaop

GPVPPSTALRYLIEELVNITQNQKAPLCNGSMVWSINLTAGMYCAALESLINVSGCSAIEKTQ
RMLSGFCPHKVSAGQFSSLHVRDTKIEVAQFVKDLLLHLKKLFREGRFNESKYGPPCPPCPAP
EFEGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSQEDPEVQFNWYVDGVEVHNAKTKPRE
EQFQSTYRVVSVLTVLHQDWLNGKEYKCKVSNKGLPSSIEKTISKAKGQPREPQVYTLPPSQE
EMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSRLTVDKSRW
QEGNVFSCSVMHEALHNHYTQKSLSLSLGKMALIVLGGVAGLLLFIGLGIFFAVSLSKMLKKR
SPLTTGVYVKMPPTEPECEKQFQPYFIPINGGGRVKFSRSADAPAYQQGQNQLYNELNLGR
REEYDVLDKRRGRDPEMGGKPRRKNPQEGLYNELQKDKMAEAYSEIGMKGERRRGKGHD
GLYQGLSTATKDTYDALHMQALPPR

IL13
IgG4(L235E,N297Q)
CD4 transmembrane
CTLA4
(Gly)3
Zeta

FIG. 16B

CD6scFvop(VH-VL)-IgG4op(L235E,N297Q)-CD4tmop-41BB-Zetaop-T2A-CD19t

MLLLVTSLLLCELPHPAFLLIPEVQLVESGGGLVKPGGSLKLSCAASGFKFSRYAMSWVRQAP
GKRLEWVATISSGGSYIYYPDSVKGRFTISRDNVKNTLYLQMSSLRSEDTAMYYCARRDYDLD
YFDSWGQGTLVTVSSGSTSGGGSGGGSGGGGSSDIQMTQSPSSLSASVGDRVTITCKASRD
IRSYLTWYQQKPGKAPKTLIYYATSLADGVPSRFSGSGSGQDYSLTISSLESDDTATYYCLQHG
ESPFTFGSGTKLEIKRAESKYGPPCPPCPAPEFEGGPSVFLFPPKPKDTLMISRTPEVTCVVVD
VSQEDPEVQFNWYVDGVEVHNAKTKPREEQFQSTYRVVSVLTVLHQDWLNGKEYKCKVS
NKGLPSSIEKTISKAKGQPREPQVYTLPPSQEEMTKNQVSLTCLVKGFYPSDIAVEWESNGQP
ENNYKTTPPVLDSDGSFFLYSRLTVDKSRWQEGNVFSCSVMHEALHNHYTQKSLSLSLGKM
ALIVLGGVAGLLLFIGLGIFFKRGRKKLLYIFKQPFMRPVQTTQEEDGCSCRFPEEEEGGCELG
GGRVKFSRSADAPAYQQGQNQLYNELNLGRREEYDVLDKRRGRDPEMGGKPRRKNPQEG
LYNELQKDKMAEAYSEIGMKGERRRGKGHDGLYQGLSTATKDTYDALHMQALPPRLEGGG
EGRGSLLTCGDVEENPGPRMPPPRLLFFLLFLTPMEVRPEEPLVVKVEEGDNAVLQCLKGTS
DGPTQQLTWSRESPLKPFLKLSLGLPGLGIHMRPLAIWLFIFNVSQQMGGFYLCQPGPPSEK
AWQPGWTVNVEGSGELFRWNVSDLGGLGCGLKNRSSEGPSSPSGKLMSPKLYVWAKDRP
EIWEGEPPCVPPRDSLNQSLSQDLTMAPGSTLWLSCGVPPDSVSRGPLSWTHVHPKGPKSL
LSLELKDDRPARDMWVMETGLLLPRATAQDAGKYYCHRGNLTMSFHLEITARPVLWHWLL
RTGGWKVSAVTLAYLIFCLCSLVGILHLQRALVLRRKR

GMCSFRa signal peptide
CD6scFvOP(VH_VL)
IgG4(L235E,N297Q)
CD4 transmembrane
4-1BB
(Gly)3
Zeta
T2A
CD19t

FIG. 17A

CD6scFvop(VH-VL)-IgG4op(L235E,N297Q)-CD4tmop-41BB-Zetaop

EVQLVESGGGLVKPGGSLKLSCAASGFKFSRYAMSWVRQAPGKRLEWVATISSGGSYIYYPD
SVKGRFTISRDNVKNTLYLQMSSLRSEDTAMYYCARRDYDLDYFDSWGQGTLVTVSSGSTS
GGGSGGGSGGGGSSDIQMTQSPSSLSASVGDRVTITCKASRDIRSYLTWYQQKPGKAPKTLI
YYATSLADGVPSRFSGSGSGQDYSLTISSLESDDTATYYCLQHGESPFTFGSGTKLEIKRAESKY
GPPCPPCPAPEFEGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSQEDPEVQFNWYVDGVE
VHNAKTKPREEQFQSTYRVVSVLTVLHQDWLNGKEYKCKVSNKGLPSSIEKTISKAKGQPRE
PQVYTLPPSQEEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLY
SRLTVDKSRWQEGNVFSCSVMHEALHNHYTQKSLSLSLGKMALIVLGGVAGLLLFIGLGIFFK
RGRKKLLYIFKQPFMRPVQTTQEEDGCSCRFPEEEEGGCELGGGRVKFSRSADAPAYQQGQ
NQLYNELNLGRREEYDVLDKRRGRDPEMGGKPRRKNPQEGLYNELQKDKMAEAYSEIGMK
GERRRGKGHDGLYQGLSTATKDTYDALHMQALPPR

CD6scFvOP(VH_VL)
IgG4(L235E,N297Q)
CD4 transmembrane
4-1BB
(Gly)3
Zeta

FIG. 17B

CD6scFvop(VH-VL)-IgG4op(L235E,N297Q)-CD4tmop-CTLA4-Zetaop-T2A-CD19t

MLLLVTSLLLCELPHPAFLLIPEVQLVESGGGLVKPGGSLKLSCAASGFKFSRYAMSWVRQAP
GKRLEWVATISSGGSYIYYPDSVKGRFTISRDNVKNTLYLQMSSLRSEDTAMYYCARRDYDLD
YFDSWGQGTLVTVSSGSTSGGGSGGGSGGGGSSDIQMTQSPSSLSASVGDRVTITCKASRD
IRSYLTWYQQKPGKAPKTLIYYATSLADGVPSRFSGSGSGQDYSLTISSLESDDTATYYCLQHG
ESPFTFGSGTKLEIKRAESKYGPPCPPCPAPEFEGGPSVFLFPPKPKDTLMISRTPEVTCVVVD
VSQEDPEVQFNWYVDGVEVHNAKTKPREEQFQSTYRVVSVLTVLHQDWLNGKEYKCKVS
NKGLPSSIEKTISKAKGQPREPQVYTLPPSQEEMTKNQVSLTCLVKGFYPSDIAVEWESNGQP
ENNYKTTPPVLDSDGSFFLYSRLTVDKSRWQEGNVFSCSVMHEALHNHYTQKSLSLSLGKM
ALIVLGGVAGLLLFIGLGIFFAVSLSKMLKKRSPLTTGVYVKMPPTEPECEKQFQPYFIPINGGG
RVKFSRSADAPAYQQGQNQLYNELNLGRREEYDVLDKRRGRDPEMGGKPRRKNPQEGLY
NELQKDKMAEAYSEIGMKGERRRGKGHDGLYQGLSTATKDTYDALHMQALPPRLEGGGE
GRGSLLTCGDVEENPGPRMPPPRLLFFLLFLTPMEVRPEEPLVVKVEEGDNAVLQCLKGTSD
GPTQQLTWSRESPLKPFLKLSLGLPGLGIHMRPLAIWLFIFNVSQQMGGFYLCQPGPPSEKA
WQPGWTVNVEGSGELFRWNVSDLGGLGCGLKNRSSEGPSSPSGKLMSPKLYVWAKDRPE
IWEGEPPCVPPRDSLNQSLSQDLTMAPGSTLWLSCGVPPDSVSRGPLSWTHVHPKGPKSLL
SLELKDDRPARDMWVMETGLLLPRATAQDAGKYYCHRGNLTMSFHLEITARPVLWHWLLR
TGGWKVSAVTLAYLIFCLCSLVGILHLQRALVLRRKR

GMCSFRa signal peptide
CD6scFvOP(VH_VL)
IgG4(L235E,N297Q)
CD4 transmembrane
CTLA4
(Gly)3
Zeta
T2A
CD19t

FIG. 18A

CD6scFvop(VH-VL)-IgG4op(L235E,N297Q)-CD4tmop-CTLA4-Zetaop

EVQLVESGGGLVKPGGSLKLSCAASGFKFSRYAMSWVRQAPGKRLEWVATISSGGSYIYYPD
SVKGRFTISRDNVKNTLYLQMSSLRSEDTAMYYCARRDYDLDYFDSWGQGTLVTVSSGSTS
GGGSGGGSGGGGSSDIQMTQSPSSLSASVGDRVTITCKASRDIRSYLTWYQQKPGKAPKTLI
YYATSLADGVPSRFSGSGSGQDYSLTISSLESDDTATYYCLQHGESPFTFGSGTKLEIKRAESKY
GPPCPPCPAPEFEGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSQEDPEVQFNWYVDGVE
VHNAKTKPREEQFQSTYRVVSVLTVLHQDWLNGKEYKCKVSNKGLPSSIEKTISKAKGQPRE
PQVYTLPPSQEEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLY
SRLTVDKSRWQEGNVFSCSVMHEALHNHYTQKSLSLSLGKMALIVLGGVAGLLLFIGLGIFFA
VSLSKMLKKRSPLTTGVYVKMPPTEPECEKQFQPYFIPINGGGRVKFSRSADAPAYQQGQN
QLYNELNLGRREEYDVLDKRRGRDPEMGGKPRRKNPQEGLYNELQKDKMAEAYSEIGMKG
ERRRGKGHDGLYQGLSTATKDTYDALHMQALPPR

CD6scFvOP(VH_VL)
IgG4(L235E,N297Q)
CD4 transmembrane
CTLA4
(Gly)3
Zeta

FIG. 18B

CD6scFvop(VH-VL)mhi-IgG4op(L235E,N297Q)-CD4tmop-41BB-Zetaop-T2A-CD19t

MLLLVTSLLLCELPHPAFLLIPEVQLVESGGGLVKPGGSLKLSCAASGFKFSRYAMSWVRQAP
GKGLEWVATISSGGSYIYYPDSVKGRFTISRDNVKNTLYLQMSSLRSEDTAMYYCARRDYDL
DYFDSWGQGTLVTVSSGSTSGGGSGGGSGGGGSGDIQMTQSPSSLSASVGDRVTITCKASR
DIRSYLTWYQQKPGKAPKTLIYYATSLADGVPSRFSGSGSGQDYSLTISSLESDDTATYYCLQH
GESPFTFGSGTKMEIKRAESKYGPPCPPCPAPEFEGGPSVFLFPPKPKDTLMISRTPEVTCVVV
DVSQEDPEVQFNWYVDGVEVHNAKTKPREEQFQSTYRVVSVLTVLHQDWLNGKEYKCKVS
NKGLPSSIEKTISKAKGQPREPQVYTLPPSQEEMTKNQVSLTCLVKGFYPSDIAVEWESNGQP
ENNYKTTPPVLDSDGSFFLYSRLTVDKSRWQEGNVFSCSVMHEALHNHYTQKSLSLSLGKM
ALIVLGGVAGLLLFIGLGIFFKRGRKKLLYIFKQPFMRPVQTTQEEDGCSCRFPEEEEGGCELG
GGRVKFSRSADAPAYQQGQNQLYNELNLGRREEYDVLDKRRGRDPEMGGKPRRKNPQEG
LYNELQKDKMAEAYSEIGMKGERRRGKGHDGLYQGLSTATKDTYDALHMQALPPRLEGGG
EGRGSLLTCGDVEENPGPRMPPPRLLFFLLFLTPMEVRPEEPLVVKVEEGDNAVLQCLKGTS
DGPTQQLTWSRESPLKPFLKLSLGLPGLGIHMRPLAIWLFIFNVSQQMGGFYLCQPGPPSEK
AWQPGWTVNVEGSGELFRWNVSDLGGLGCGLKNRSSEGPSSPSGKLMSPKLYVWAKDRP
EIWEGEPPCVPPRDSLNQSLSQDLTMAPGSTLWLSCGVPPDSVSRGPLSWTHVHPKGPKSL
LSLELKDDRPARDMWVMETGLLLPRATAQDAGKYYCHRGNLTMSFHLEITARPVLWHWLL
RTGGWKVSAVTLAYLIFCLCSLVGILHLQRALVLRRKR

GMCSFRa signal peptide
CD6scFv(VH_VL)OP-high
IgG4(L235E,N297Q)
CD4 transmembrane
4-1BB
(Gly)3
Zeta
T2A
CD19t

FIG. 19A

CD6scFvop(VH-VL)mhi-IgG4op(L235E,N297Q)-CD4tmop-41BB-Zetaop

EVQLVESGGGLVKPGGSLKLSCAASGFKFSRYAMSWVRQAPGKGLEWVATISSGGSYIYYP
DSVKGRFTISRDNVKNTLYLQMSSLRSEDTAMYYCARRDYDLDYFDSWGQGTLVTVSSGST
SGGGSGGGSGGGGSGDIQMTQSPSSLSASVGDRVTITCKASRDIRSYLTWYQQKPGKAPKT
LIYYATSLADGVPSRFSGSGSGQDYSLTISSLESDDTATYYCLQHGESPFTFGSGTKMEIKRAES
KYGPPCPPCPAPEFEGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSQEDPEVQFNWYVDG
VEVHNAKTKPREEQFQSTYRVVSVLTVLHQDWLNGKEYKCKVSNKGLPSSIEKTISKAKGQP
REPQVYTLPPSQEEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFF
LYSRLTVDKSRWQEGNVFSCSVMHEALHNHYTQKSLSLSLGKMALIVLGGVAGLLLFIGLGIF
FKRGRKKLLYIFKQPFMRPVQTTQEEDGCSCRFPEEEEGGCELGGGRVKFSRSADAPAYQQ
GQNQLYNELNLGRREEYDVLDKRRGRDPEMGGKPRRKNPQEGLYNELQKDKMAEAYSEIG
MKGERRRGKGHDGLYQGLSTATKDTYDALHMQALPPR

CD6scFv(VH_VL)OP - high
IgG4(L235E,N297Q)
CD4 transmembrane
4-1BB
(Gly)3
Zeta

FIG. 19B

CD6scFvop(VH-VL)mhi-IgG4op(L235E,N297Q)-CD4tmop-CTLA4-Zetaop-T2A-CD19t

MLLLVTSLLLCELPHPAFLLIPEVQLVESGGGLVKPGGSLKLSCAASGFKFSRYAMSWVRQAP
GKGLEWVATISSGGSYIYYPDSVKGRFTISRDNVKNTLYLQMSSLRSEDTAMYYCARRDYDL
DYFDSWGQGTLVTVSSGSTSGGGSGGGSGGGGSGDIQMTQSPSSLSASVGDRVTITCKASR
DIRSYLTWYQQKPGKAPKTLIYYATSLADGVPSRFSGSGSGQDYSLTISSLESDDTATYYCLQH
GESPFTFGSGTKMEIKRAESKYGPPCPPCPAPEFEGGPSVFLFPPKPKDTLMISRTPEVTCVVV
DVSQEDPEVQFNWYVDGVEVHNAKTKPREEQFQSTYRVVSVLTVLHQDWLNGKEYKCKVS
NKGLPSSIEKTISKAKGQPREPQVYTLPPSQEEMTKNQVSLTCLVKGFYPSDIAVEWESNGQP
ENNYKTTPPVLDSDGSFFLYSRLTVDKSRWQEGNVFSCSVMHEALHNHYTQKSLSLSLGKM
ALIVLGGVAGLLLFIGLGIFFAVSLSKMLKKRSPLTTGVYVKMPPTEPECEKQFQPYFIPINGGG
RVKFSRSADAPAYQQGQNQLYNELNLGRREEYDVLDKRRGRDPEMGGKPRRKNPQEGLY
NELQKDKMAEAYSEIGMKGERRRGKGHDGLYQGLSTATKDTYDALHMQALPPRLEGGGE
GRGSLLTCGDVEENPGPRMPPPRLLFFLLFLTPMEVRPEEPLVVKVEEGDNAVLQCLKGTSD
GPTQQLTWSRESPLKPFLKLSLGLPGLGIHMRPLAIWLFIFNVSQQMGGFYLCQPGPPSEKA
WQPGWTVNVEGSGELFRWNVSDLGGLGCGLKNRSSEGPSSPSGKLMSPKLYVWAKDRPE
IWEGEPPCVPPRDSLNQSLSQDLTMAPGSTLWLSCGVPPDSVSRGPLSWTHVHPKGPKSLL
SLELKDDRPARDMWVMETGLLLPRATAQDAGKYYCHRGNLTMSFHLEITARPVLWHWLLR
TGGWKVSAVTLAYLIFCLCSLVGILHLQRALVLRRKR

GMCSFRa signal peptide
CD6scFv(VH_VL)OP - high
IgG4(L235E,N297Q)
CD4 transmembrane
CTLA4
(Gly)3
Zeta
T2A
CD19t

FIG. 20A

CD6scFvop(VH-VL)mhi-IgG4op(L235E,N297Q)-CD4tmop-CTLA4-Zetaop

EVQLVESGGGLVKPGGSLKLSCAASGFKFSRYAMSWVRQAPGKGLEWVATISSGGSYIYYP
DSVKGRFTISRDNVKNTLYLQMSSLRSEDTAMYYCARRDYDLDYFDSWGQGTLVTVSSGST
SGGGSGGGSGGGGSGDIQMTQSPSSLSASVGDRVTITCKASRDIRSYLTWYQQKPGKAPKT
LIYYATSLADGVPSRFSGSGSGQDYSLTISSLESDDTATYYCLQHGESPFTFGSGTKMEIKRAES
KYGPPCPPCPAPEFEGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSQEDPEVQFNWYVDG
VEVHNAKTKPREEQFQSTYRVVSVLTVLHQDWLNGKEYKCKVSNKGLPSSIEKTISKAKGQP
REPQVYTLPPSQEEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFF
LYSRLTVDKSRWQEGNVFSCSVMHEALHNHYTQKSLSLSLGKMALIVLGGVAGLLLFIGLGIF
FAVSLSKMLKKRSPLTTGVYVKMPPTEPECEKQFQPYFIPINGGGRVKFSRSADAPAYQQGQ
NQLYNELNLGRREEYDVLDKRRGRDPEMGGKPRRKNPQEGLYNELQKDKMAEAYSEIGMK
GERRRGKGHDGLYQGLSTATKDTYDALHMQALPPR

CD6scFv(VH_VL)OP - high
IgG4(L235E,N297Q)
CD4 transmembrane
CTLA4
(Gly)3
Zeta

FIG. 20B

CD19scFvop(VH-VL)-IgG4op(L235E,N297Q)-CD4tmop-CTLA4-Zetaop-T2A-EGFRt

MLLLVTSLLLCELPHPAFLLIPDIQMTQTTSSLSASLGDRVTISCRASQDISKYLNWYQQKPDG
TVKLLIYHTSRLHSGVPSRFSGSGSGTDYSLTISNLEQEDIATYFCQQGNTLPYTFGGGTKLEIT
GSTSGSGKPGSGEGSTKGEVKLQESGPGLVAPSQSLSVTCTVSGVSLPDYGVSWIRQPPRKG
LEWLGVIWGSETTYYNSALKSRLTIIKDNSKSQVFLKMNSLQTDDTAIYYCAKHYYYGGSYAM
DYWGQGTSVTVSSESKYGPPCPPCPAPEFEGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVS
QEDPEVQFNWYVDGVEVHNAKTKPREEQFQSTYRVVSVLTVLHQDWLNGKEYKCKVSNK
GLPSSIEKTISKAKGQPREPQVYTLPPSQEEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPEN
NYKTTPPVLDSDGSFFLYSRLTVDKSRWQEGNVFSCSVMHEALHNHYTQKSLSLSLGKMALI
VLGGVAGLLLFIGLGIFFAVSLSKMLKKRSPLTTGVYVKMPPTEPECEKQFQPYFIPINGGGRV
KFSRSADAPAYQQGQNQLYNELNLGRREEYDVLDKRRGRDPEMGGKPRRKNPQEGLYNEL
QKDKMAEAYSEIGMKGERRRGKGHDGLYQGLSTATKDTYDALHMQALPPRLEGGGEGRG
SLLTCGDVEENPGPRMLLLVTSLLLCELPHPAFLLIPRKVCNGIGIGEFKDSLSINATNIKHFKNC
TSISGDLHILPVAFRGDSFTHTPPLDPQELDILKTVKEITGFLLIQAWPENRTDLHAFENLEIIRG
RTKQHGQFSLAVVSLNITSLGLRSLKEISDGDVIISGNKNLCYANTINWKKLFGTSGQKTKIISN
RGENSCKATGQVCHALCSPEGCWGPEPRDCVSCRNVSRGRECVDKCNLLEGEPREFVENSE
CIQCHPECLPQAMNITCTGRGPDNCIQCAHYIDGPHCVKTCPAGVMGENNTLVWKYADA
GHVCHLCHPNCTYGCTGPGLEGCPTNGPKIPSIATGMVGALLLLLVVALGIGLFM

GMCSFRa signal peptide
CD19scFvop
IgG4(L235E,N297Q)
CD4 transmembrane
CTLA4
(Gly)3
Zeta
T2A
EGFRt

FIG. 21A

CD19scFvop(VH-VL)-IgG4op(L235E,N297Q)-CD4tmop-CTLA4-Zetaop

DIQMTQTTSSLSASLGDRVTISCRASQDISKYLNWYQQKPDGTVKLLIYHTSRLHSGVPSRFS
GSGSGTDYSLTISNLEQEDIATYFCQQGNTLPYTFGGGTKLEITGSTSGSGKPGSGEGSTKGEV
KLQESGPGLVAPSQSLSVTCTVSGVSLPDYGVSWIRQPPRKGLEWLGVIWGSETTYYNSALK
SRLTIIKDNSKSQVFLKMNSLQTDDTAIYYCAKHYYYGGSYAMDYWGQGTSVTVSSESKYGP
PCPPCPAPEFEGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSQEDPEVQFNWYVDGVEVH
NAKTKPREEQFQSTYRVVSVLTVLHQDWLNGKEYKCKVSNKGLPSSIEKTISKAKGQPREPQ
VYTLPPSQEEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSR
LTVDKSRWQEGNVFSCSVMHEALHNHYTQKSLSLSLGKMALIVLGGVAGLLLFIGLGIFFAVS
LSKMLKKRSPLTTGVYVKMPPTEPECEKQFQPYFIPINGGGRVKFSRSADAPAYQQGQNQLY
NELNLGRREEYDVLDKRRGRDPEMGGKPRRKNPQEGLYNELQKDKMAEAYSEIGMKGERR
RGKGHDGLYQGLSTATKDTYDALHMQALPPR

CD19scFvop
IgG4(L235E,N297Q)
CD4 transmembrane
CTLA4
(Gly)3
Zeta

FIG. 21B

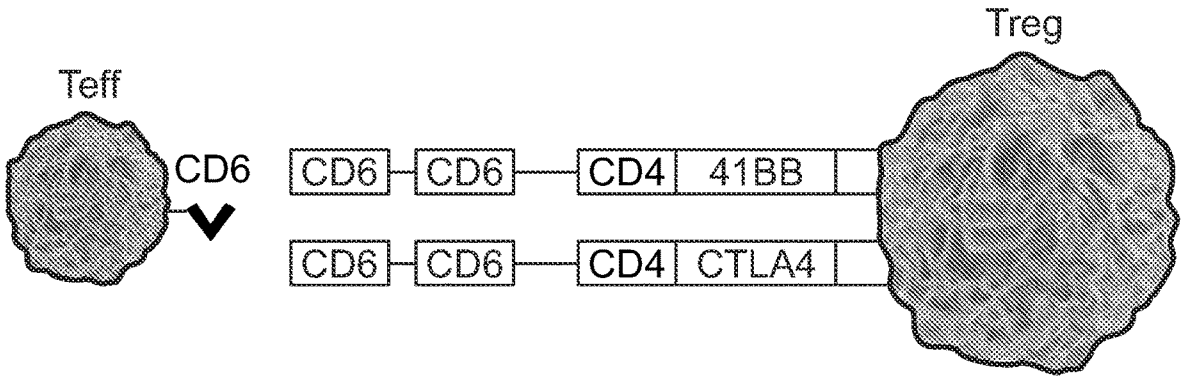


FIG. 22A

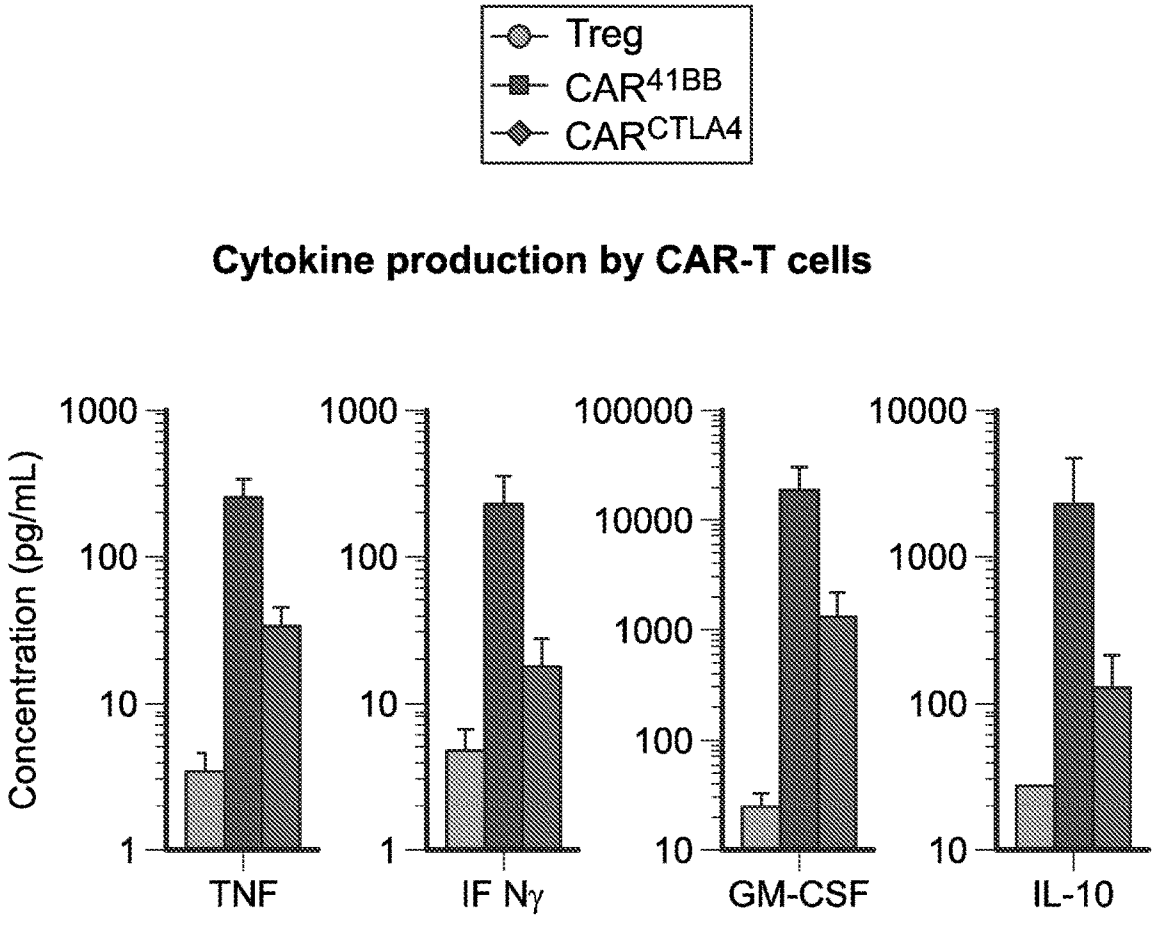


FIG. 22B

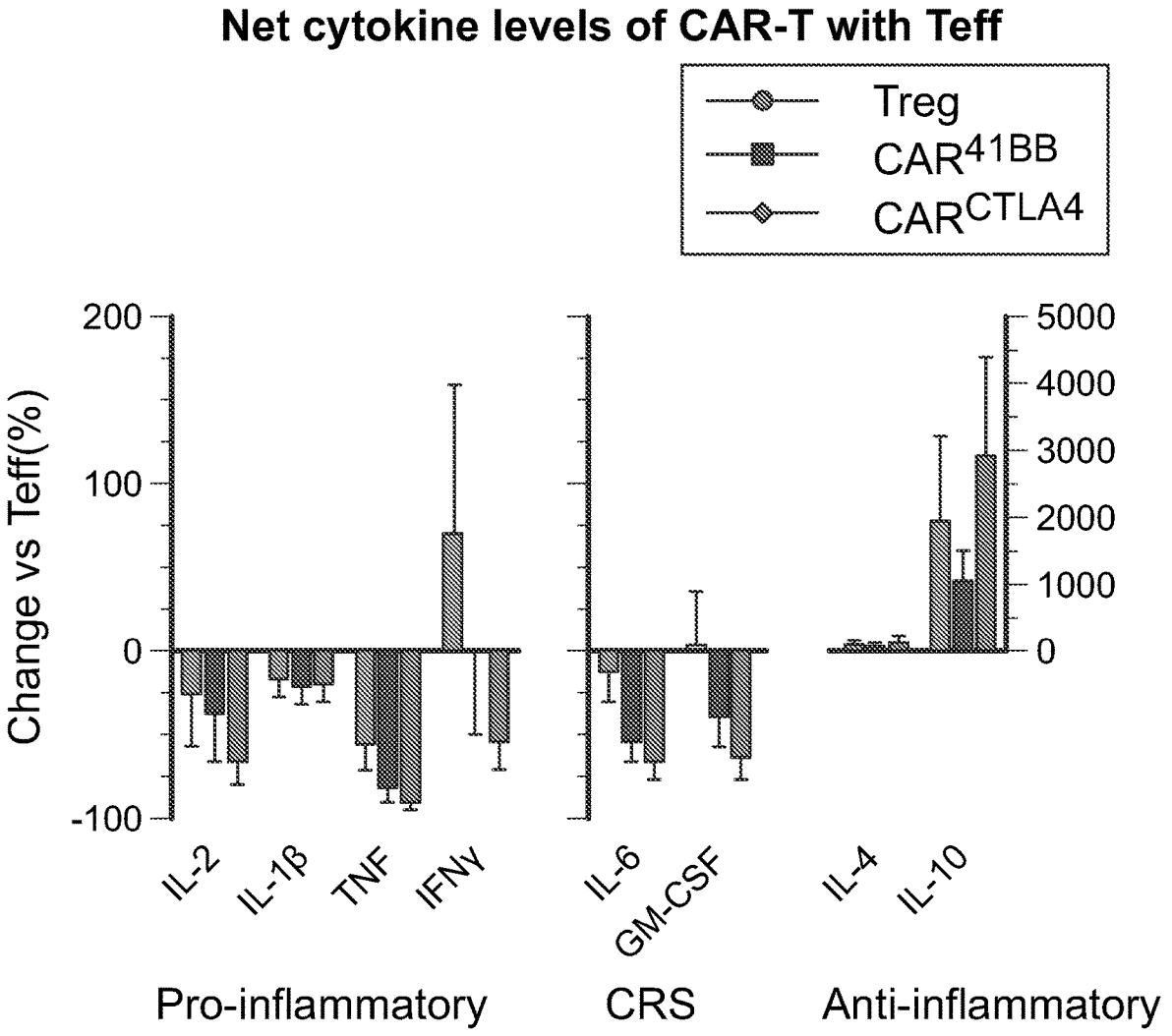

Net cytokine levels of CAR-T with Teff
Treg
CAR41BB
CARCTLA4
Change vs Teff(%)
200
100
0
-100
5000
4000
3000
2000
1000
0
IL-2
IL-1β
TNF
IFNγ
IL-6
GM-CSF
IL-4
IL-10
Pro-inflammatory
CRS
Anti-inflammatory

FIG. 22C

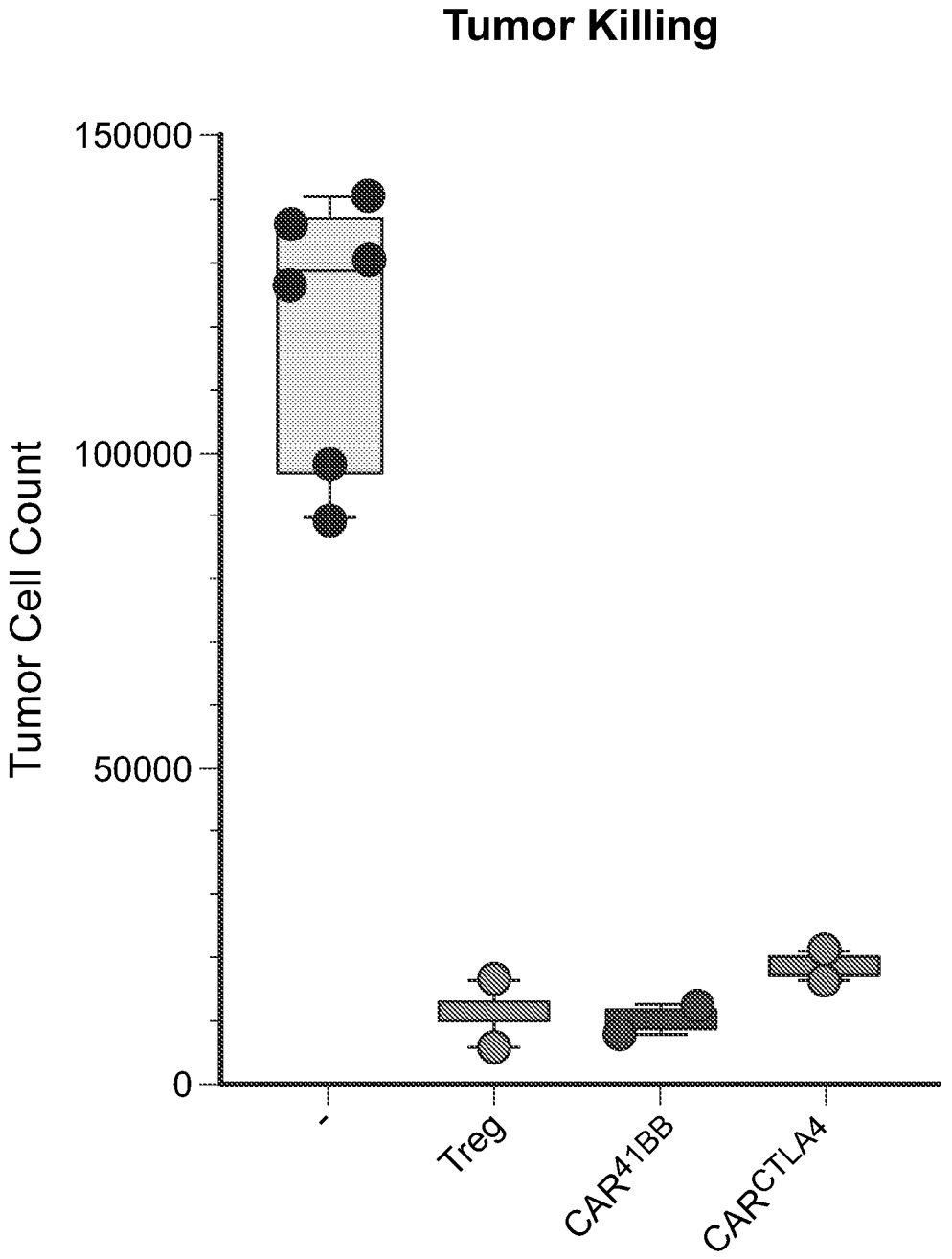

Tumor Killing
Tumor Cell Count
150000
100000
50000
0
-
Treg
CAR41BB
CARCTLA4

FIG. 22D

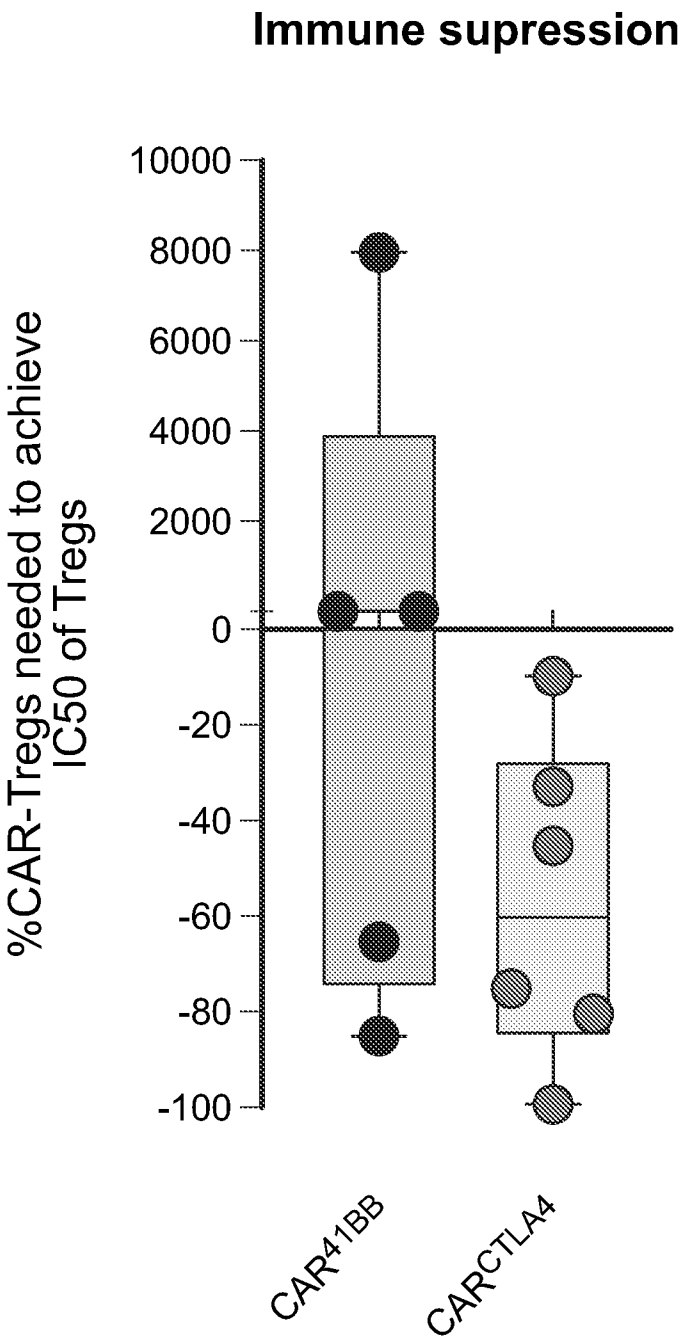

Immune supression
%CAR-Tregs needed to achieve IC50 of Tregs
10000
8000
6000
4000
2000
0
-20
-40
-60
-80
-100
CAR41BB
CARCTLA4

FIG. 22E

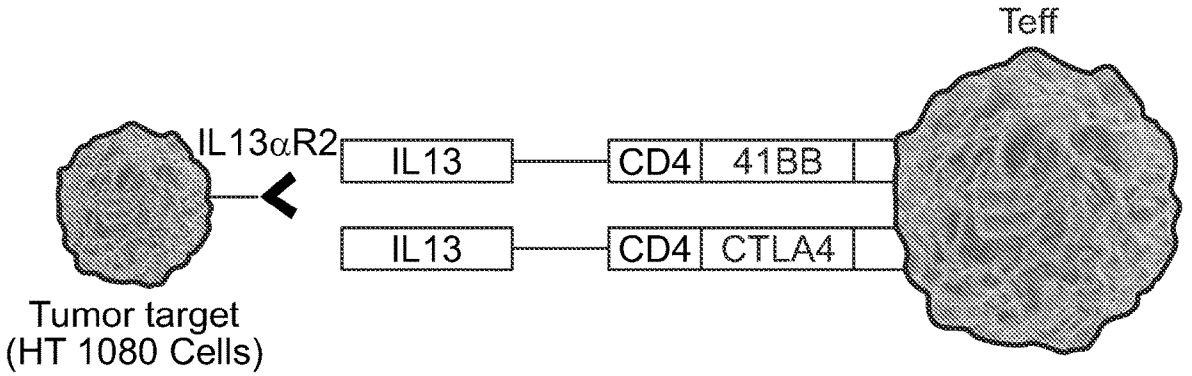

Teff
IL13αR2
IL13
CD4
41BB
IL13
CD4
CTLA4
Tumor target
(HT 1080 Cells)

FIG. 23A

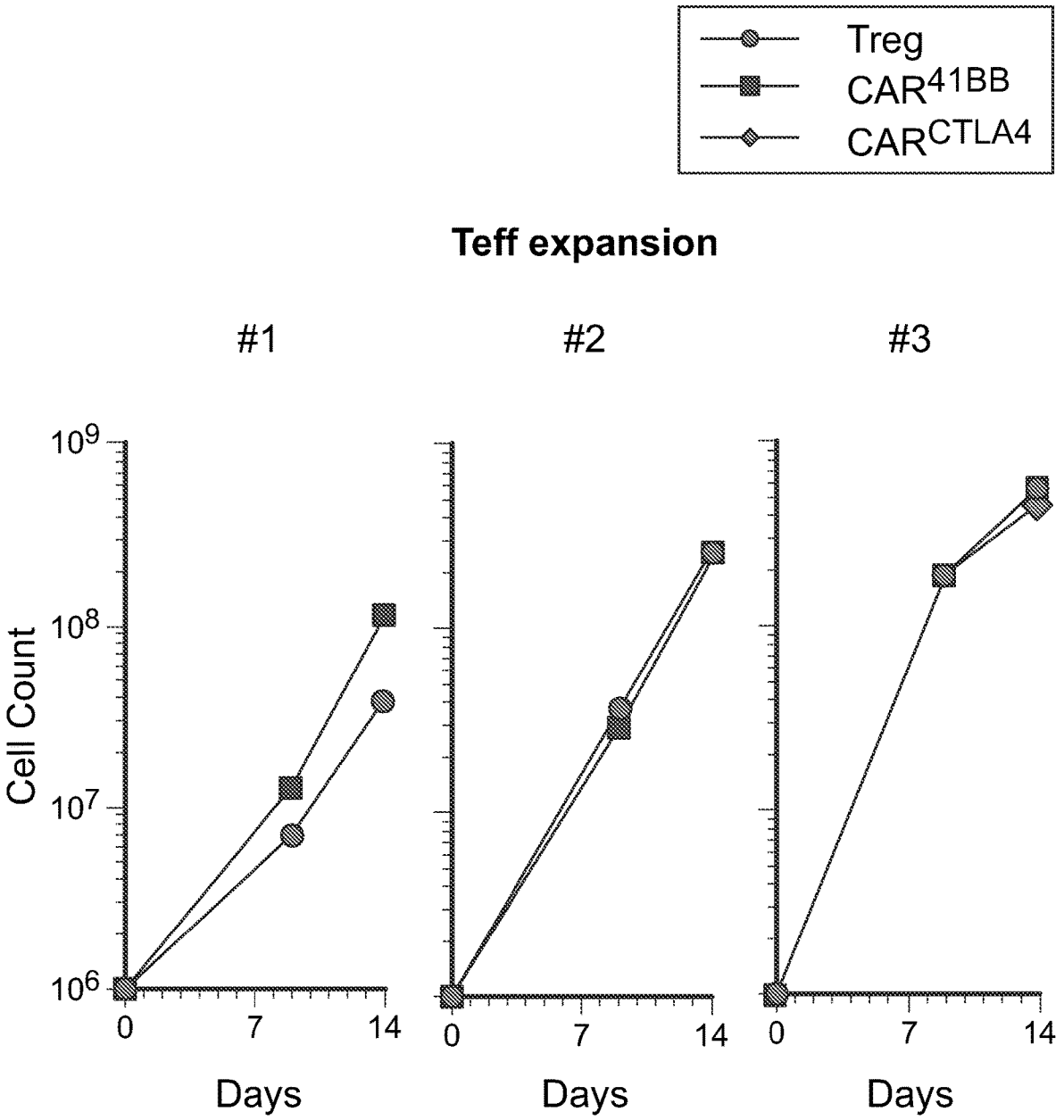

Treg
CAR41BB
CARCTLA4
Teff expansion
#1
#2
#3
Cell Count
10^9
10^8
10^7
10^6
0
7
14
Days

FIG. 23B

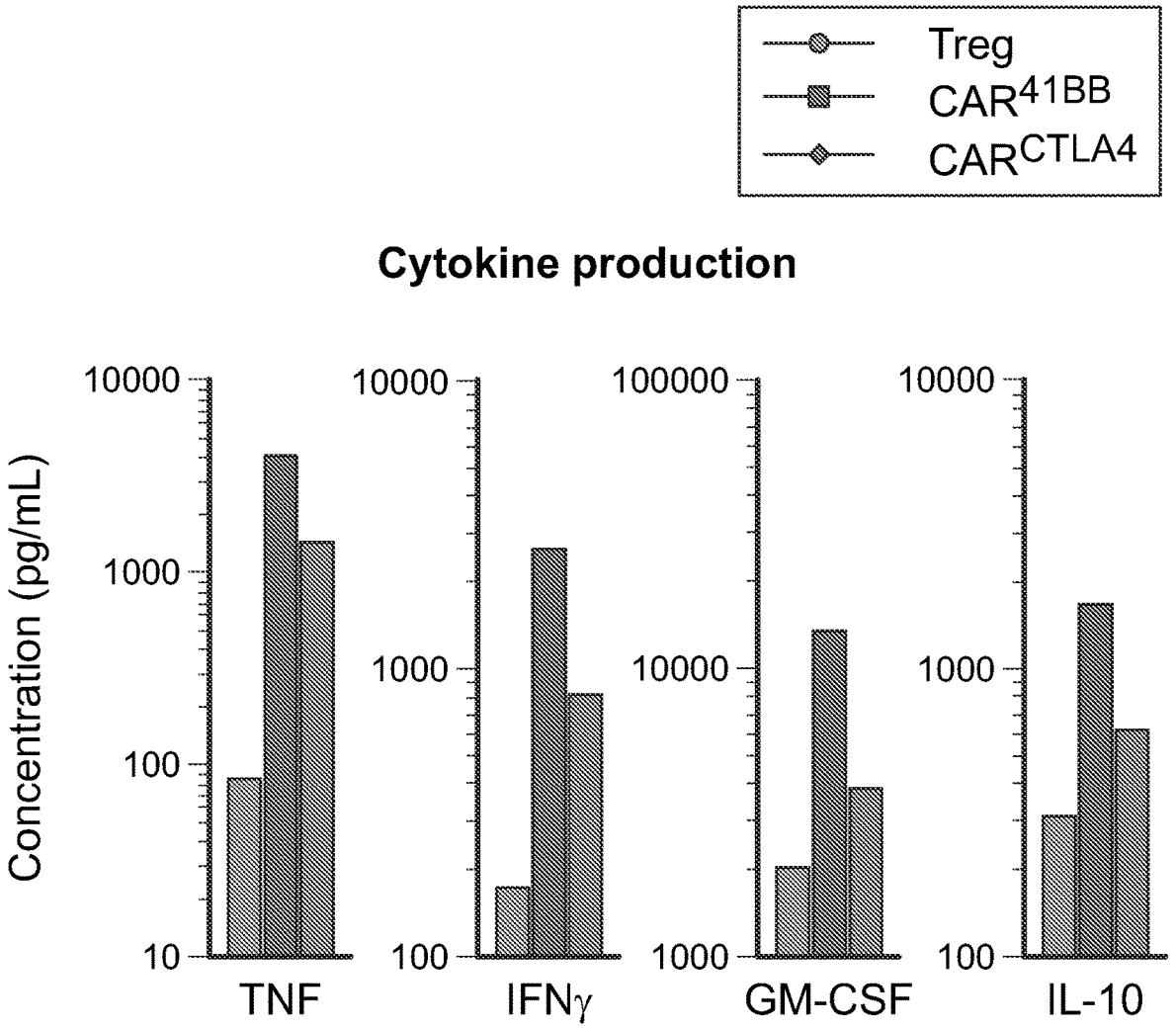

Treg
CAR41BB
CARCTLA4
Cytokine production
Concentration (pg/mL)
10000
1000
100
10
TNF
IFNγ
100000
GM-CSF
IL-10

FIG. 23C

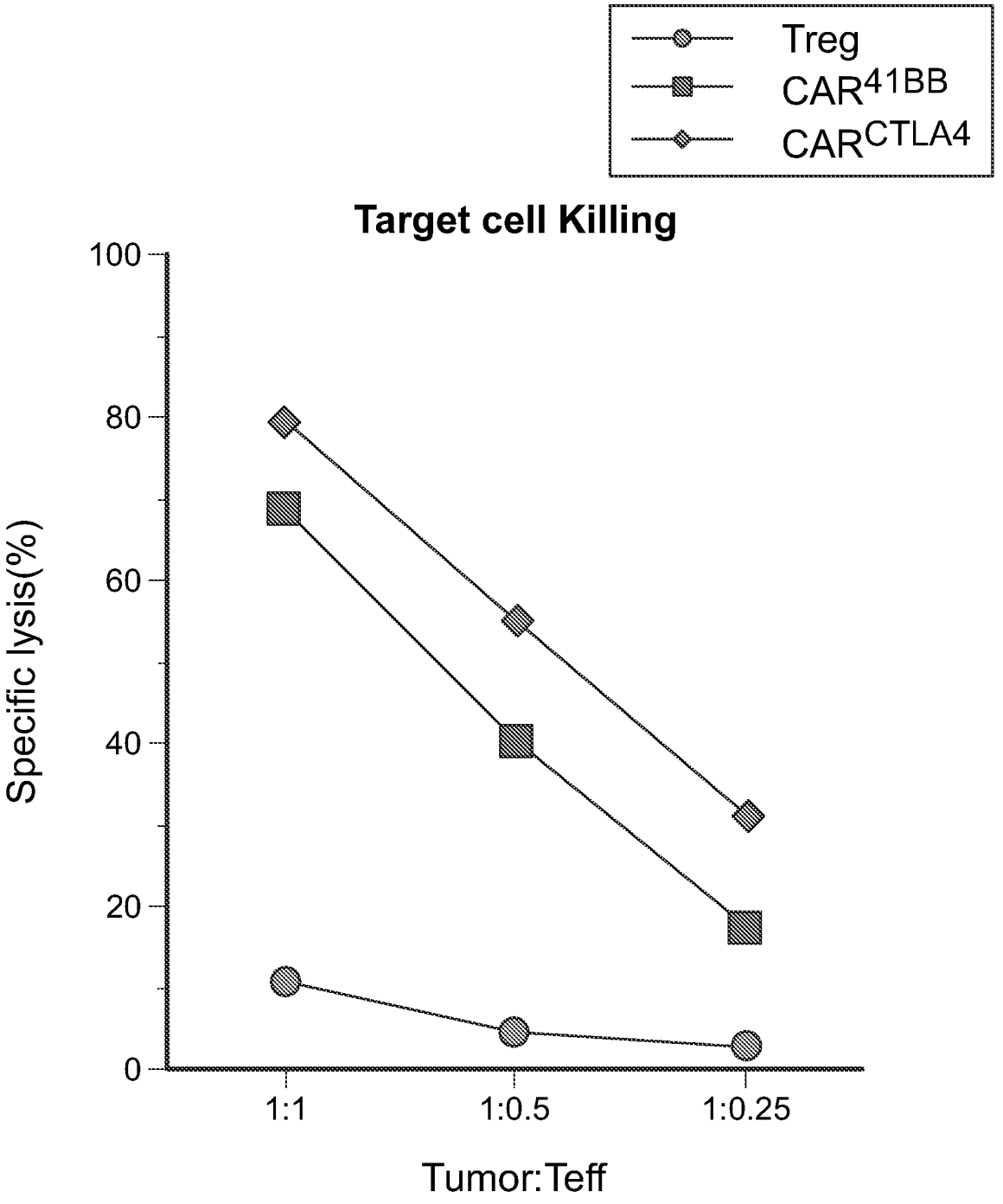
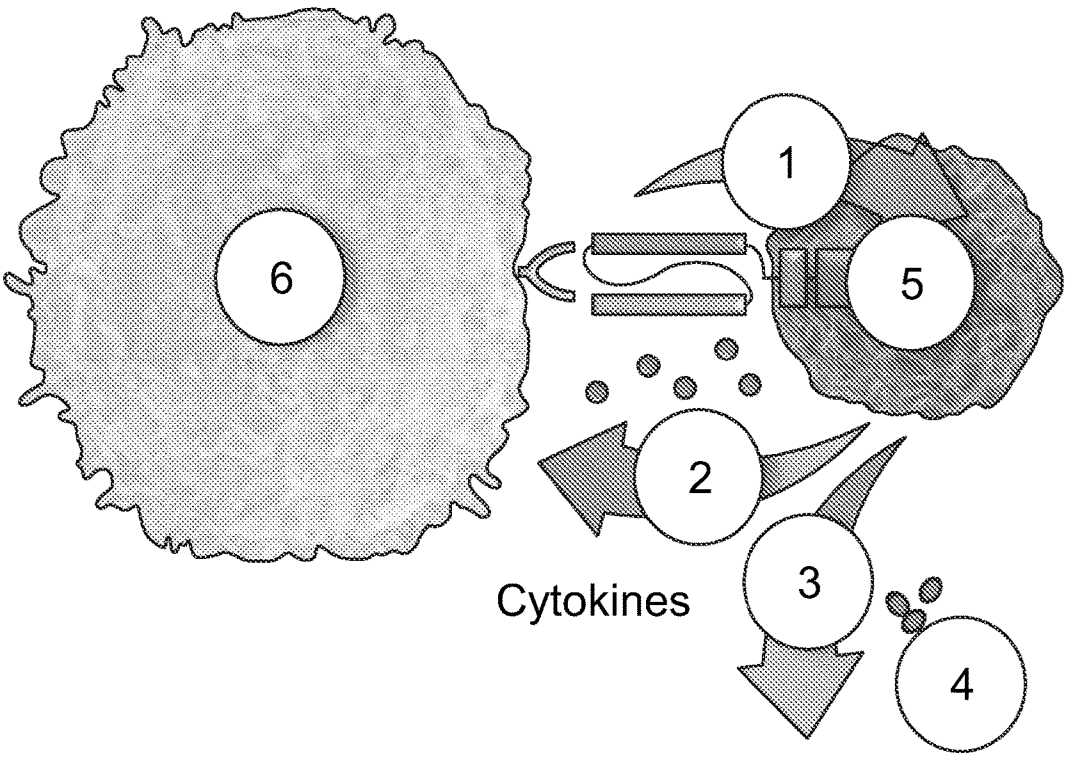

Treg
CAR41BB
CARCTLA4
Target cell Killing
100
80
60
40
20
0
Specific lysis(%)
1:1
1:0.5
1:0.25
Tumor:Teff

FIG. 23D



1. CAR transduced T cells produced a tuned activation signaling upon antigen-specific recognition
2. Blunted cytokine release
3. Less off target effects (reduction CRS)
4. Minimized local and systematic tissue damage
5. CAR T-cell life extension
6. Equal or increased anti-cancer efficiency

FIG. 24

METHODS OF MAKING AND USING REGULATORY T CELLS AND EFFECTOR T CELLS HAVING CHIMERIC ANTIGEN RECEPTORS TARGETED TO CD6, CD19, AND/OR AN IL-13R FOR TREATMENT OF AUTOIMMUNE DISORDERS AND CANCERS

CLAIM OF PRIORITY

[0001] This application claims the benefit of U.S. Provisional Application Ser. No. 62/955,389, filed on Dec. 30, 2019. The entire contents of the foregoing are incorporated herein by reference.

BACKGROUND

[0002] The majority of CAR domains are single chain variable fragments (scFvs) derived from antibody sequences that exploit the specificity of antibody binding to particular antigens. There are few examples of CAR domains derived from receptor ligands, and despite some notable successes, the identification and validation of novel CAR tumor targeting domains remains a major challenge in the field. There are also notable variations in the severity of side effects amongst other reason to improve CAR therapies.

SUMMARY

[0003] Described herein are chimeric antigen receptors (CARs) or polypeptides targeted to CD6, CD19, and/or an IL-13 receptor (IL-13R; e.g., IL-13Rα2). The CD6 CAR, CD19 CAR, and IL-13 CAR can be expressed in regulatory T cells (Treg) or effector cells (Teff).

[0004] In some embodiments, CD6 CAR Tregs target the CD6 molecule overexpressed in pro-inflammatory T-cells, e.g., in Type 1 Diabetes (T1D) patients. This approach is in contrast to targeting beta-cell antigens, which may induce additional damage to pancreatic islets. In some embodiments, the current approach employs a CAR or polypeptide that includes an scFv derived from Itolizumab, an immunomodulatory anti-CD6 monoclonal antibody (U.S. Pat. No. 6,572,857). A CD6 CAR or polypeptide that includes a CD152 (CTLA-4) cytoplasmic domain (in addition to CD3 zeta) can drive inhibitory signaling in transduced host cells and reinforce the immunomodulatory activity of CAR-Tregs. In some cases, the binding between an CAR or polypeptide described herein and the antigen is of intermediate affinity. In some embodiments, the K_D of the interaction is between about 10 nM and 140 nM. For example, the binding between a CD6 CAR or polypeptide expressed by a Treg and CD6 are relatively low affinity with respect to known interactions with CD6. Without being bound by theory, this can avoid over-activation of adoptively transferred cells and extend their lifespan. In some embodiments, the CARs or polypeptides described herein are expressed in an $CD6^{low/-}$ subset of Tregs. In some cases a CAR or polypeptide described herein expressed in Tregs can have an improved safety profile compared to a CAR or polypeptide expressed in T effector cells (Teff). Without being bound by theory, this may be because Tregs are less likely to trigger adverse cytokine release syndrome. In some embodiments, Tregs can produce anti-inflammatory molecules such as IDO, TGF-beta, and IL-10. In some embodiments, the Tregs expressing a CAR or polypeptide described herein unexpectedly display potent tumor cell cytotoxicity, maintaining the distinct features of human regulatory cells such as persistent FOXP3 expression. Without being bound by theory, this potent anti-tumor effect is in addition to or rather than suppressing the immune response. In some embodiments, the use of a Treg described herein for human cancer therapy or human autoimmune therapy has the following advantages over the traditional CAR approach hosted in effector T-cells or NK cells are based on: (1) equal or superior adaptive cytolytic capacity of tumor cells expressing the CAR ligand; (2) the composite anti-tumor response including the CAR driven anti-tumor specific response combined with the capability of Treg competing for nutrients while accessing the tumor microenvironment; (3) Lower or negligible life-threatening cytokine release syndrome (CRS), due to the intrinsic nature of Treg producing anti-inflammatory molecules such as IDO, TGF beta, or IL-10; (4) Additionally, Treg are less susceptible to lymphocyte exhaustion resulting in an extended persistence and improved efficacy of adoptive immunotherapy.

[0005] Provided herein, inter alia, are cells, nucleic acids, proteins, methods, and compositions for treatment of an autoimmune disease or a cancer. In some embodiments, the autoimmune disease is associated with reduced islet cell (e.g., beta cell) function, viability, or survival. In some embodiments, the autoimmune disease includes a subject's immune system attacking the subject's islet cells (e.g., beta cells). Also provided herein are, inter alia, compositions useful for the treatment of certain autoimmune diseases and/or cancers. In some embodiments, novel CAR-T cells targeting the human CD6 molecule, the human CD19 molecule, and/or IL-13Rα2 are provided herein. In some embodiments, chimeric antigen receptors (CARs) or polypeptides described herein exhibit different ranges of affinities for the CD6 molecule, CD19 molecule, and/or IL-13Rα2. In some embodiments, these CARs or polypeptides are expressed in different types of human cells, including T regulatory cells (Tregs or Treg), Natural Killer (NK) cells and effector T cells (Teffs or Teff). In some embodiments, an observed K_D of a CAR or polypeptide described herein for its target/ligand is about 1, 5, 10, 15, 20, 25, 30, 35, 40, 45, 50, 55, 60, 65, 70, 75, 80, 85, 90, 95, 100, 105, 110, 115, 120, 125, 130, 135, 140, 145, or 150 nM. In some embodiments, an observed K_D of the CAR or polypeptide for its target is about 1-10, 5-15, 10-20, 5-25, 1-30, 5-30, 10-30, 1-40, 5-40, 10-40, 30-40, 5-50, 10-50, 30-50, 30-60, 5-75, 10-75, 30-75, 1-100, 5-100, 10-100, 25-100, 30-100, 1-125, 5-125, 10-125, 25-125, 30-125, 1-150, 5-150, 10-150, 25-150, or 30-150 nM.

[0006] In some embodiments, provided herein is an isolated nucleic acid encoding a protein including a single chain variable fragment (scFv) targeted to CD6. In some embodiments, provided herein is an isolated nucleic acid encoding a protein including a single chain variable fragment (scFv) targeted to CD19. In some embodiments, provided herein is an isolated nucleic acid encoding a protein including IL-13. In some embodiments, these nucleic acids are optimized.

[0007] In some embodiments, a vector including a nucleic acid described herein, including embodiments thereof, is provided. In some embodiments, the vector can be a viral vector (lentivirus vector) or any suitable vector known in the art.

[0008] In some embodiments, a T lymphocyte including the vector provided herein, including embodiments thereof, is provided. In some embodiments, a T lymphocyte is a Treg or a Teff.

[0009] In some embodiments, a recombinant protein including a single chain variable fragment (scFv) targeted to CD6, including embodiments thereof, is provided. In some embodiments, a recombinant protein including a single chain variable fragment (scFv) targeted to CD19, including embodiments thereof, is provided. In some embodiments, a recombinant protein including IL-13, or variants thereof, is provided.

[0010] In some embodiments, described herein is a nucleic acid molecule comprising a nucleotide sequence encoding a chimeric antigen receptor (CAR), wherein the chimeric antigen receptor comprises: a targeting domain, a spacer, a transmembrane domain, a co-stimulatory domain (also called "signaling domain"), and a CD3 (signaling domain.

[0011] In some embodiments: the transmembrane domain is selected from: a CD4 transmembrane domain or variant thereof having 1-5 amino acid modifications, a CD8 transmembrane domain or variant thereof having 1-5 amino acid modifications, a CD28 transmembrane domain or a variant thereof having 1-5 amino acid modifications; the spacer comprises 20-150 amino acids and is located between the tumor-targeting domains and the transmembrane domain; the transmembrane domain is a CD4 transmembrane domain or variant thereof having 1-5 amino acid modifications; the transmembrane domain is a CD4 transmembrane domain; the chimeric antigen receptor comprises a transmembrane domain selected from: a CD4 transmembrane domain or variant thereof having 1-2 amino acid modifications, a CD8 transmembrane domain or variant thereof having 1-2 amino acid modifications, a CD28 transmembrane domain or a variant thereof having 1-2 amino acid modifications; the spacer comprises an IgG hinge region; the spacer comprises 10-50 amino acids; the costimulatory domain comprises a CD28 costimulatory domain, an 4-1BB costimulatory domain, or an CTLA-4 cytoplasmic domain, or a variant of any of the foregoing having 1-5 amino acid modifications; the CD3ζ signaling domain or a variant thereof having 1-5 amino acid; a linker of 3 to 15 amino acids is located between the 4-1BB costimulatory domain and the CD3 (signaling domain, the CD28 costimulatory domain and the CD3 (signaling domain, or the CTLA-4 costimulatory domain and the CD3 (signaling domain, or variant thereof, the CAR comprises the amino acid sequence of any one of SEQ ID NOS: 29-33, 83-100, or a variant thereof having 1-5 amino acid modifications; the targeting domain comprises the amino acid sequence of any one of SEQ ID NOS: 1, 34-42, 101-113, or a variant thereof having 1-5 amino acid modifications; the nucleic acid molecule of claim **1**. In some embodiments, the nucleic acid sequences and/or amino acid sequences described herein have been optimized.

[0012] In various embodiments, the chimeric antigen receptor comprises: a IL-13 (e.g., an IL-13 comprising the amino acid sequence GPVPPSTALRYLIEELVNITQNQKAPLCNGSMVWSINLTAGMYCAALESLINVSGCSAIE KTQRMLSGFCPHKVSAGQFSSLHVRDTKIEVAQFVKDLLLHLKKLFREGRFN (SEQ ID NO:101) or variant thereof with 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10 single amino acid substitutions). In some embodiments, the CAR comprises: a variant of a human IL13 having 1-10 amino acid modification that increase binding specificity for IL13Rα2 versus IL13Rα1 (e.g. E13Y).

[0013] In some embodiments, a CD19-targeted CAR (CD19 CAR, also called anti-CD19 CAR herein) described herein include a CD19 targeting scFv (e.g., an scFv comprising the amino acid sequence:

(SEQ ID NO: 102)
DIQMTQTTSSLSASLGDRVTISCRASQDISKYLNWYQQKPDGTVKLLIYH

TSRLHSGVPSRFSGSGSGTDYSLTISNLEQEDIATYFCQQGNTLPYTFGG

GTKLEITGSTSGSGKPGSGEGSTKGEVKLQESGPGLVAPSQSLSVTCTVS

GVSLPDYGVSWIRQPPRKGLEWLGVIWGSETTYYNSALKSRLTIIKDNSK

SQVFLKMNSLQTDDTAIYYCAKHYYYGGSYAMDYWGQGTSVTVSS

or variant thereof with 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10 single amino acid substitutions or comprising the sequence DIQMTQTTSSLSASLGDRVTISCRASQDISKY-LNWYQQKPDGTVKLLIYHTSRLHSGVPS RFSGSGSGTDYSLTISNLEQEDIATYFCQQGNTLPYTF (SEQ ID NO:103) or variant thereof with 1, 2, 3, 4, or 5 single amino acid substitutions and the sequence TKLEITGSTSGSGKPGSGEGSTK-GEVKLQESGPGLVAP-SQSLSVTCTVSGVSLPDYGVSW IRQPPRKGLEW-LGVIWGSETTYYNSALKSRLTIIKDNSKSQVFLKMNS LQTDDTAIYYCA KHYYYGGSYAMDYWGQGTSVTVSS (SEQ ID NO:104) or variant thereof with 1, 2, 3, 4, or single amino acid substitutions joined by a flexible linker.

[0014] In some embodiments, a CD6-targeted CAR (CD6 CAR, also called anti-CD6 CAR herein) described herein include a CD6 targeting scFv (e.g., an scFv comprising the amino acid sequence:

(SEQ ID NO: 105)
EVQLVESGGGLVKPGGSLKLSCAASGFKFSRYAMSWVRQAPGKRLEWVAT

ISSGGSYIYYPDSVKGRFTISRDNVKNTLYLQMSSLRSEDTAMYYCARRD

YDLDYFDSWGQGTLVTVSSGSTSGGGSGGGSGGGGSSDIQMTQSPSSLSA

SVGDRVTITCKASRDIRSYLTWYQQKPGKAPKTLIYYATSLADGVPSRFS

GSGSGQDYSLTISSLESDDTATYYCLQHGESPFTFGSGTKLEIKRA

or variant thereof with 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10 single amino acid substitutions or comprising the sequence EVQLVESGGGLVKPGGSLKLSCAASGFKFSRYAM-SWVRQAPGKRLEWVATISSGGSYI YYPDSVKGRFTISRDNVKNTLYLQMSSLRSED-TAMYYCARRDYDLDYFDSWGQGTLV TV (SEQ ID NO:106) or variant thereof with 1, 2, 3, 4, or 5 single amino acid substitutions and the sequence DIQMTQSPSSL-SASVGDRVTITCKASRDIR-SYLTWYQQKPGKAPKTLIYYATSLADGVPS RFSGSGSGQDYSLTISSLESDDTATYY-CLQHGESPFTFGSGTKLEIKRA (SEQ ID NO:107) or variant thereof with 1, 2, 3, 4, or 5 single amino acid substitutions joined by a flexible linker.

[0015] In some embodiments, a CD6-targeted CAR (CD6 CAR, also called anti-CD6 CAR herein) described herein include a CD6 targeting scFv (e.g., an scFv comprising the amino acid sequence:

(SEQ ID NO: 108)
EVQLVESGGGLVKPGGSLKLSCAASGFKFSRYAMSWVRQAPGKGLEWVAT

ISSGGSYIYYPDSVKGRFTISRDNVKNTLYLQMSSLRSEDTAMYYCARRD

YDLDYFDSWGQGTLVTVSSGSTSGGGSGGGSGGGGSGDIQMTQSPSSLSA

SVGDRVTITCKASRDIRSYLTWYQQKPGKAPKTLIYYATSLADGVPSRFS

GSGSGQDYSLTISSLESDDTATYYCLQHGESPFTFGSGTKMEIKRA

or variant thereof with 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10 single amino acid substitutions or comprising the sequence EVQLVESGGGLVKPGGSLKLSCAASGFKFSRYAMSWVRQAPGKGLEWVATISSGGSYI YYPDSVKGRFTISRDNVKNTLYLQMSSLRSEDTAMYYCARRDYDLDYFDSWGQGTLV TVSS (SEQ ID NO:109) or variant thereof with 1, 2, 3, 4, or 5 single amino acid substitutions and the sequence DIQMTQSPSSLSASVGDRVTITCKASRDIRSYLTWYQQKPGKAPKTLIYYATSLADGVPS RFSGSGSGQDYSLTISSLESDDTATYYCLQHGESPFTFGSGTKMEIKRA (SEQ ID NO:110) or variant thereof with 1, 2, 3, 4, or 5 single amino acid substitutions joined by a flexible linker.

[0016] In some embodiments, a CD6-targeted CAR (CD6 CAR, also called anti-CD6 CAR herein) described herein include a CD6 targeting scFv (e.g., an scFv comprising the amino acid sequence:

(SEQ ID NO: 111)
DIQMTQSPSSLSASVGDRVTITCKASRDIRSYLTWYQQKPGKAPKTLIYY

ATSLADGVPSRFSGSGSGQDYSLTISSLESDDTATYYCLQHGESPFTFGS

GTKLEIKRAGSTSGGGSGGGSGGGGSSEVQLVESGGGLVKPGGSLKLSCA

ASGFKFSRYAMSWVRQAPGKRLEWVATISSGGSYIYYPDSVKGRFTISRD

NVKNTLYLQMSSLRSEDTAMYYCARRDYDLDYFDSWGQGTLVTVSS

or variant thereof with 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10 single amino acid substitutions or comprising the sequence DIQMTQSPSSLSASVGDRVTITCKASRDIRSYLTWYQQKPGKAPKTLIYYATSLADGVPS RFSGSGSGQDYSLTISSLESDDTATYYCLQHGESPFTFGSGTKMEIKRA (SEQ ID NO:112) or variant thereof with 1, 2, 3, 4, or 5 single amino acid substitutions and the sequence EVQLVESGGGLVKPGGSLKLSCAASGFKFSRYAMSWVRQAPGKGLEWVATISSGGSYI YYPDSVKGRFTISRDNVKNTLYLQMSSLRSEDTAMYYCARRDYDLDYFDSWGQGTLV TVSS (SEQ ID NO:113) or variant thereof with 1, 2, 3, 4, or 5 single amino acid substitutions joined by a flexible linker.

[0017] Also disclosed herein is: a viral vector comprising a nucleic acid molecule described herein (e.g., a lentiviral vector or other suitable vector known in the art); a population of human T cells (e.g., a population comprising central memory T cells; a population comprising effector T cells; a population of Treg cells; etc.) transduced by a vector comprising a nucleic acid molecule described herein.

[0018] In some embodiments, a T lymphocyte (e.g. a Treg cell or a Teff cell), including a recombinant protein provided herein, including embodiments thereof, is provided. In some embodiments, a T lymphocyte (e.g. a Treg cell or a Teff cell), including a CAR provided herein, including embodiments thereof, is provided.

[0019] In some embodiments, provided herein is a method of treating an autoimmune disease. In some embodiments, the method includes administering to a subject in need thereof an effective amount of a T-lymphocyte, e.g. a Treg cell of Teff cell, as described herein, including embodiments thereof.

[0020] Also described herein is a method of treating can tumor or cancer that expresses a CD6 and/or an CD19 and/or an IL-13 receptor (e.g., IL-13Rα2): including, e.g., glioblastoma, primary brain tumors and gliomas (glioblastoma multiforme WHO Grade IV, anaplastic astrocytoma WHO Grade III, low-grade astrocytoma WHO Grade II, pilocytic astrocytoma WHO Grade I, other ungraded gliomas, oligodendroglioma, gliosarcoma, ganglioglioma, meningioma, ependymona), neuroectodermal tumors (medulloblastoma, neuroblastoma, ganglioneuroma, melanoma (metastatic), melanoma (primary), pheochromocytoma, Ewing's sarcoma, primitive neuroectodermal tumors, small cell lung carcinoma, Schwannoma), other brain tumors (epidermoid cysts, brain tumors of unknown pathology, pituitary gland of glioblastoma multiforme pt., metastatic tumors to brain of unknown tissue origin), melanoma, melanoma metastases, breast cancer, breast cancer metastases, kidney cancer, kidney cancer metastases, liver cancer, liver cancer metastases, lung cancer, lung cancer metastases, lymphoma, lymphoma metastases, ovarian cancer, ovarian cancer metastases, pancreatic cancer, pancreatic cancer metastases, prostate cancer, prostate cancer metastases, colorectal cancer, colorectal cancer metastases, combinations thereof, and the like, in a patient comprising administering a population of autologous or allogeneic human T cells transduced by a vector comprising a nucleic acid molecule described herein. In various embodiments: a chimeric antigen receptor described herein is administered locally or systemically; in some embodiments, a method of treatment includes cells expressing one or more of a CD6 receptor and/or an CD19 receptor and/or IL-13Rα2, and the cells are cancerous cells; and a chimeric antigen receptor described herein is administered by single or repeat dosing.

[0021] IL-13Rα2 is highly expressed in several human tumors associated with poor prognosis, including primary brain tumors (e.g., gliomas (e.g., anaplastic astrocytoma (AA-grade III) and glioblastoma multiforme (GBM-grade IV)), pancreatic cancer, colorectal cancer, etc.) (Davis F G, McCarthy B J. Epidemiology of brain tumors. Curr Opin Neural. 2000; 13:635-640; Davis F G, Malinski N, Haenszel W, et al. Primary brain tumor incidence rates in four United States regions, 1985-1989: a pilot study. Neuroepidemiology. 1996; 15:103-112; Smith M A, Freidlin B, Ries L A, Simon R. Increased incidence rates but no space-time clustering of childhood astrocytoma in Sweden, 1973-1992: a population-based study of pediatric brain tumors. Cancer. 2000; 88:1492-1493; Davis F G, Freels S, Grutsch J, Barias S, Brem S. Survival rates in patients with primary malignant brain tumors stratified by patient age and tumor histological type: an analysis based on Surveillance, Epidemiology, and End Results (SEER) data, 1973-1991. J Neurosurg. 1998, 88:1-10; Fujisawa T, Joshi B, Nakajima A, et al (2009) A

novel role of interleukin-13 receptor alpha2 in pancreatic cancer invasion and metastasis. Cancer Res 69: 8678-8685; Zhou R, et al. Interleukin-13 and its receptors in colorectal cancer, Biomedical Reports 1: 687-690, 2013).

[0022] Teff cells expressing a CAR targeting CD19 can be useful in treatment of cancers such as B cell lymphomas, as well as other cancer that expresses. Thus, this disclosure includes methods for treating cancer using T cells expressing a CAR described herein.

[0023] Type 1 diabetes mellitus (T1D) precipitates from the autoimmune attack of pancreatic beta cells thereby resulting in a loss of functional beta cell mass. Functional beta cell mass is impacted positively by processes that increase the number and size of beta cells and negatively by those that deplete the numbers of cells (i.e., apoptosis, necrosis, and other modes of cell death). In addition, beta cell secretory function and capacity is a substantial determinant of functional beta cell mass. In T1D patients, the proliferative and regenerative potential of adult and human islets is low. Thus, it is important to prevent or delay the autoimmune attack and resultant destruction of beta cells, and to establish methods to promote beta cell mass expansion, increase beta cell survival, and/or enhance the function of existing/remaining beta cells, including engaging cellular repair mechanisms to restore functional beta cell mass. However, therapeutic strategies aiming to simultaneously target the pancreatic islet-infiltrating lymphocytes along with protecting and replenishing the functional beta cell mass are limited.

[0024] Described herein is a nucleic acid encoding a chimeric antigen receptor (CAR) or polypeptide comprising a single chain variable fragment (scFv) targeted to CD6, a hinge region, a transmembrane domain, a CTLA4 signaling domain or a 41BB signaling domain, and a CD3 zeta signaling domain. Also described here is a nucleic acid encoding a chimeric antigen receptor (CAR) or polypeptide comprising a single chain variable fragment (scFv) targeted to CD19, a hinge region, a transmembrane domain, a CTLA4 signaling domain or a 41BB signaling domain, and a CD3 zeta signaling domain. Also described herein is a nucleic acid encoding a chimeric antigen receptor (CAR) or polypeptide comprising an IL-13, a hinge region, a transmembrane domain, a CTLA4 signaling domain or a 41BB signaling domain, and a CD3 zeta signaling domain. In some embodiments, the transmembrane domain comprises a CD4 transmembrane domain or a variant thereof, a CD8 transmembrane domain or a variant thereof, a CD28 transmembrane domain or a variant thereof, or a CD3 transmembrane domain or a variant thereof. In some embodiments, the CAR or polypeptide comprises or consists of an amino acid sequence at least 90, 95, 96, 97, 98, or 99% identical to any of SEQ ID Nos: 83-90 and 93-100. In some embodiments, the CAR or polypeptide comprises or consists of an amino acid sequence of any of SEQ ID Nos: 83-90 and 93-100 with no more than 5 single amino acid substitutions. In some embodiments, the CAR or polypeptide comprises or consists of an amino acid sequence at least 90, 95, 96, 97, 98, or 99% identical to any of SEQ ID Nos: 114-115. In some embodiments, the CAR or polypeptide comprises or consists of an amino acid sequence of any of SEQ ID Nos: 114-115 with no more than 5 single amino acid substitutions. In some embodiments, the CAR or polypeptide comprises or consists of an amino acid sequence at least 90, 95, 96, 97, 98, or 99% identical to any of SEQ ID Nos: 91-92. In some embodiments, the CAR or polypeptide comprises or consists of an amino acid sequence of any of SEQ ID Nos: 91-92 with no more than 5 single amino acid substitutions. In some embodiments, the scFv is as depicted in FIG. **1**-**5** or **17**A-**20**B. In some embodiments, t the scFv is as depicted in FIG. **21**A-**21**B. In some embodiments, the IL-13 is as depicted in FIG. **16**A-**16**B. In some embodiments, t the scFv comprises any of SEQ ID NOs:105-113. In some embodiments, t the scFv comprises any of SEQ ID NOs:102-104. In some embodiments, t the IL-13 comprises SEQ ID NO: 101. Also described herein is a vector comprising a nucleic acid described herein. In some embodiments, the vector is a viral vector. In some embodiments, the vector is a lentivirus vector or any suitable vector known in the art.

[0025] Also described herein is a population of T cells transduced by a vector comprising a nucleic acid described herein. Also described herein is a population of T cells expressing a CAR or polypeptide encoded by a nucleic acid described herein. In some embodiments, the T cells are regulatory T cells or effector T cells. In some embodiments, the population of Treg cells are such that least 70%, 80%, or 90% of the cells are $CD4^+$ $CD25^{high}$, $CD4^+$ $CD25^{high}$ $CD127^{low}$, $CD4^+$ $CD25^{high}$ $CD127^-$, $CD4^+$ $CD25^{high}$ $CD6^{low}$, $CD4^+$ $CD25^{high}$ $CD6^-$, $CD4^+$ $CD25^{high}$ $CD127^{low}$ $CD6^{low}$, $CD4^+$ $CD25^{high}$ $CD127^-$ $CD6^{low}$, $CD4^+$ $CD25^{high}$ $CD127^{low}$ $CD6^-$, $CD4^+$ $CD25^{high}$ $CD127^-$ $CD6^-$, $CD3^+$ $CD6^{low}$, or $CD3^+$ $CD6^-$. In some embodiments, the population of T cells are human T cells. In some embodiments, the population of T cells are autologous human T cells or allogenic human T cells.

[0026] Also described herein is a chimeric antigen receptor (CAR) or polypeptide comprising a single chain variable fragment (scFv) targeted to CD6, a hinge region, a transmembrane domain, a CTLA4 signaling domain or a 41BB signaling domain, and a CD3 zeta signaling domain. Also described herein is a chimeric antigen receptor (CAR) or polypeptide comprising a single chain variable fragment (scFv) targeted to CD19, a hinge region, a transmembrane domain, a CTLA4 signaling domain or a 41BB signaling domain, and a CD3 zeta signaling domain. Also described herein is a chimeric antigen receptor (CAR) or polypeptide comprising an IL-13, a hinge region, a transmembrane domain, a CTLA4 signaling domain or a 41BB signaling domain, and a CD3 zeta signaling domain. In some embodiments, the transmembrane domain comprises a CD4 transmembrane domain or a variant thereof, a CD8 transmembrane domain or a variant thereof, a CD28 transmembrane domain or a variant thereof, or a CD3ζ transmembrane domain or a variant thereof. In some embodiments, the scFv is as depicted in FIG. **1**-**5** or **17**A-**20**B. In some embodiments, the scFv is as depicted in FIGS. **21**A-**21**B. In some embodiments, the IL-13 is as depicted in FIGS. **16**A-**16**B. In some embodiments, the scFv comprises any of SEQ ID NOs:105-113. In some embodiments, the scFv comprises SEQ ID NOs:105. In some embodiments, the scFv comprises SEQ ID NOs:106. In some embodiments, the scFv comprises any of SEQ ID NOs:102-104. In some embodiments, the IL-13 comprises SEQ ID NO: 101. In some embodiments, the CAR or polypeptide comprises or consists of an amino acid sequence at least 90, 95, 96, 97, 98, or 99% identical to any of SEQ ID Nos: 83-90 and 93-100. In some embodiments, the CAR or polypeptide comprises or consists of an amino acid sequence of any of SEQ ID Nos: 83-90 and 93-100 with no more than 5 single amino acid substitutions.

In some embodiments, the CAR or polypeptide comprises or consists of an amino acid sequence at least 90, 95, 96, 97, 98, or 99% identical to any of SEQ ID Nos: 114-115. In some embodiments, the CAR or polypeptide comprises or consists of an amino acid sequence of any of SEQ ID Nos: 114-115 with no more than 5 single amino acid substitutions. In some embodiments, the CAR or polypeptide comprises or consists of an amino acid sequence at least 90, 95, 96, 97, 98, or 99% identical to any of SEQ ID Nos: 91-92. In some embodiments, the CAR or polypeptide comprises or consists of an amino acid sequence of any of SEQ ID Nos: 91-92 with no more than 5 single amino acid substitutions. In some embodiments, the CAR or polypeptide further comprises an intracellular T-cell signaling domain. In some embodiments, intracellular T-cell signaling domain is a CD3ζ intracellular T-cell signaling domain. In some embodiments, the CAR or polypeptide is encoded by a nucleic acid described herein.

[0027] Also described herein is a population of T cells comprising a CAR or polypeptide described herein. Also described herein is a population of T cells expressing a CAR or polypeptide. In some embodiments, the population of T cells comprise regulatory T cells. In some embodiments, the population of T cells comprise effector T cells. In some embodiments, the population of Treg cells is at least 70%, 80%, or 90% of the cells are $CD4^+$ $CD25^{high}$, $CD4^+$ $CD25^{high}$ $CD127^{low}$, $CD4^+$ $CD25^{high}$ $CD127^-$, $CD4^+$ $CD25^{high}$ $CD6^{low}$, $CD4^+$ $CD25^{high}$ $CD6^-$, $CD4^+$ $CD25^{high}$ $CD127^{low}$ $CD6^{low}$, $CD4^+$ $CD25^{high}$ $CD127^-$ $CD6^{low}$, $CD4^+$ $CD25^{high}$ $CD127^{low}$ $CD6^-$, $CD4^+$ $CD25^{high}$ $CD127^-$ $CD6^{low}$, $CD3^+$ $CD61^{low}$, or $CD3^+$ $CD6^-$. In some embodiments, at least 70%, 80%, or 90% of cells are CD6low or CD6–. In some embodiments, the population of T cells are human T cells. In some embodiments, the population of T cells are autologous human T cells or allogenic human T cells.

[0028] Also described herein are compositions comprising any of the population of T cells described herein. Also described herein are compositions comprising a population of T cells harboring a nucleic acid described herein. Also described herein are compositions comprising a population of T cells comprising a CAR or polypeptide described herein. Also described herein are compositions comprising a population of T cells expressing a CAR or polypeptide described herein. In some embodiments, the population of T cells are human T cells. In some embodiments, the population of T cells are autologous or allogenic. In some embodiments, the population of T cells are autologous human T cells or allogenic human T cells.

[0029] Also described herein is a method of treating a cancer, the method comprising administering to a subject in need thereof a population of T cells harboring a nucleic acid described herein, a population of T cells described herein, or a composition T cells described herein. In some embodiments, the population of T cells are human T cells. In some embodiments, the population of T cells are autologous or allogenic. In some embodiments, the population of T cells are autologous human T cells or allogenic human T cells. The method of claim **49**, wherein the cancer is a lymphoproliferative cancer. In some embodiments, the cancer comprises cells expressing CD6, CD19, or IL-13Rα2. In some embodiments, the cancer is a glioblastoma, primary brain tumors and gliomas (glioblastoma multiforme WHO Grade IV, anaplastic astrocytoma WHO Grade III, low-grade astrocytoma WHO Grade II, pilocytic astrocytoma WHO Grade I, other ungraded gliomas, oligodendroglioma, gliosarcoma, ganglioglioma, meningioma, ependymona), neuroectodermal tumors (medulloblastoma, neuroblastoma, ganglioneuroma, melanoma (metastatic), melanoma (primary), pheochromocytoma, Ewing's sarcoma, primitive neuroectodermal tumors, small cell lung carcinoma, Schwannoma), other brain tumors (epidermoid cysts, brain tumors of unknown pathology, pituitary gland of glioblastoma multiforme pt., metastatic tumors to brain of unknown tissue origin), melanoma, melanoma metastases, breast cancer, breast cancer metastases, kidney cancer, kidney cancer metastases, liver cancer, liver cancer metastases, lung cancer, lung cancer metastases, lymphoma, lymphoma metastases, ovarian cancer, ovarian cancer metastases, pancreatic cancer, pancreatic cancer metastases, prostate cancer, prostate cancer metastases, colorectal cancer, colorectal cancer metastases, combinations thereof. In some embodiments, the population of T cells or composition are administered in single or repeat dosing. In some embodiments, effective amount is administered to a subject. In some embodiments, at least one symptom is reduced, ameliorated, or relieved.

[0030] Also described herein is a method of treating an autoimmune disease, the method comprising administering to a subject in need thereof a population of T cells harboring a nucleic acid described herein, a population of T cells described herein, or a composition T cells described herein. In some embodiments, the population of T cells are human T cells. In some embodiments, the population of T cells are autologous or allogenic. In some embodiments, the population of T cells are autologous human T cells or allogenic human T cells. In some embodiments, the autoimmune disease is Type I Diabetes or Graft-versus-Host Disease. In some embodiments, the population of T cells or composition are administered in single or repeat dosing. In some embodiments, effective amount is administered to a subject. In some embodiments, at least one symptom is reduced, ameliorated, or relieved.

[0031] Also described herein is a method of killing, eliminating, or reducing cells expressing CD6, said method comprising administering to a subject in need thereof a population of T cells harboring a nucleic acid described herein, a population of T cells described herein, or a composition T cells described herein. In some embodiments, the population of T cells are human T cells. In some embodiments, the population of T cells are autologous or allogenic. In some embodiments, the population of T cells are autologous human T cells or allogenic human T cells. In some embodiments, the cells expressing CD6 are cancerous. In some embodiments, the population of T cells or composition are administered in single or repeat dosing. In some embodiments, effective amount is administered to a subject. In some embodiments, at least one symptom is reduced, ameliorated, or relieved.

[0032] Also described herein is a method of killing, eliminating, or reducing cells expressing CD19, said method comprising administering to a subject in need thereof a population of T cells harboring a nucleic acid described herein, a population of T cells described herein, or a composition T cells described herein. In some embodiments, the population of T cells are human T cells. In some embodiments, the population of T cells are autologous or allogenic. In some embodiments, the population of T cells are autologous human T cells or allogenic human T cells. In some embodiments, the cells expressing CD19 are cancerous. In

some embodiments, the population of T cells or composition are administered in single or repeat dosing. In some embodiments, effective amount is administered to a subject. In some embodiments, at least one symptom is reduced, ameliorated, or relieved.

[0033] Also described herein is a method of killing, eliminating, or reducing cells expressing an IL-13R (e.g. IL-13Rα2), said method comprising administering to a subject in need thereof a population of T cells harboring a nucleic acid described herein, a population of T cells described herein, or a composition T cells described herein. In some embodiments, the population of T cells are human T cells. In some embodiments, the population of T cells are autologous or allogenic. In some embodiments, the population of T cells are autologous human T cells or allogenic human T cells. In some embodiments, the cells expressing an IL-13R are cancerous. In some embodiments, the population of T cells or composition are administered in single or repeat dosing. In some embodiments, effective amount is administered to a subject. In some embodiments, at least one symptom is reduced, ameliorated, or relieved.

[0034] In some embodiments, a CAR or polypeptide described herein can include a spacer located between the targeting domain (i.e., a CD6 targeted ScFv or variant thereof, a CD19 targeted ScFv or variant thereof, an IL-13 or a variant thereof that binds an IL-13R) and the transmembrane domain. A variety of different spacers can be used. Some of them include at least portion of a human Fc region, for example a hinge portion of a human Fc region or a CH3 domain or variants thereof. Table 2 below provides various spacers that can be used in the CARs and polypeptides described herein.

[0035] Some spacer regions include all or part of an immunoglobulin (e.g., IgG1, IgG2, IgG3, IgG4) hinge region, i.e., the sequence that falls between the CH1 and CH2 domains of an immunoglobulin, e.g., an IgG4 Fc hinge or a CD8 hinge. Some spacer regions include an immunoglobulin CH3 domain (called CH3 or ΔCH2) or both a CH3 domain and a CH2 domain. The immunoglobulin derived sequences can include one or more amino acid modifications, for example, 1, 2, 3, 4 or 5 substitutions, e.g., substitutions that reduce off-target binding.

TABLE 2

Examples of Spacers

Name	Length	Sequence
a3	3 aa	AAA
linker	10 aa	GGGSSGGGSG (SEQ ID NO: 116)
IgG4 hinge (S→P) (S228P)	12 aa	ESKYGPPCPPCP (SEQ ID NO: 117)
IgG4 hinge	12 aa	ESKYGPPCPSCP (SEQ ID NO: 118)
IgG4 hinge	22 aa	ESKYGPPCPPCPGGGSSGGGSG (SEQ ID NO: 119)
(S228P)+ linker CD28 hinge	39 aa	IEVMYPPPYLDNEKSNGTIIHVK GKHLCPSPLFPGPSKP (SEQ ID NO: 120)
CD8 hinge-48aa	48 aa	AKPTTTPAPRPPTPAPTIASQPLSLR PEACRPAAGGAVHTRGLDFACD (SEQ ID NO: 121)
CD8 hinge-45aa	45aa	TTTPAPRPPTPAPTIASQPLSLRPEACR PAAGGAVHTRGLDFACD (SEQ ID NO: 122)
IgG4(HL-CH3) Also called IgG4(HL-ΔCH2) (includes S228P in hinge)	129 aa	ESKYGPPCPPC**P**GGGSSGGGSGGQPRN EPQVYTLPPSQEEMTKQVSLTCLVKGF YPSDIAVEWESNGQPENNYKTTPPVLD SDGSFFLYSRLTVDKSRWQEGNVFSCS VMHEALHNHYTQKSLSLSLGK (SEQ ID NO: 123)
IgG4(L235E, N297Q)	229 aa	ESKYGPPCPSCPAPEF**E**GGPSVFLFP PKPKDTLMISRTPEVTCVVVDVSQED PEVQFNWYVDGVEVHNAKTKPREEQF **Q**STYRVVSVLTVLHQDWLNGKEYKCK VSNKGLPSSIEKTISKAKGQPREPQV YTLPPSQEEMTKNQVSLTCLVKGFYP SDIAVEWESNGQPENNYKTTPPVLDS DGSFFLYSRLTVDKSRWQEGNVFSCS VMHEALHNHYTQKSLSLSLGK (SEQ ID NO: 124)
IgG4(S228P, L235E, N297Q)	229 aa	ESKYGPPCPPC**P**APEF**E**GGPSVFLFP PKPKDTLMISRTPEVTCVVDVSQEDP EVQFNWYVDGVEVHNAKTKPREEQF**Q** STYRVVSVVLTVLHQDWLNGKEYKCK VSNKGLPSSIEKTISKAKGQPREPQV YTLPPSQEEMTKNQVSLTCLVKGFYP SDIAVEWESNGQPENNYKTTPPVLDS DGSFFLYSRLTVDKSRWQEGNVFSCS VMHEALHNHYTQKSLSLSLGK (SEQ ID NO: 125)
IgG4(CH3) Also called IgG4(ΔCH2)	107 aa	GQPREPQVYTLPPSQEEMTKNQVSLT CLVKGFYPSDIAVEWESNGQPENNYK TTPPVLDSDGSFFLYSRLTVDKSRWQ EGNVFSCSVMHEALHNHYTQKSLSLS LGK (SEQ ID NO: 126)

[0036] The hinge/linker region can also comprise an IgG4 hinge region having the sequence ESKYGPPCPSCP (SEQ ID NO:118) or ESKYGPPCPPCP (SEQ ID NO:117). The hinge/linger region can also comprise the sequence ESKYGPPCPPCP (SEQ ID NO: 117) followed by the linker sequence GGGSSGGGSG (SEQ ID NO:116) followed by IgG4 CH3 sequence GQPREPQVYTLPPSQEEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLD SDGSFFLYSRLTVDKSRWQEGNVFSCSVMHEALHNHYTQKSLSLSLGK (SEQ ID NO:126). Thus, the entire linker/spacer region can comprise the sequence:

(SEQ ID NO: 125)
ESKYGPPCPPCPGGGSSGGGSGGQPREPQVYTLPPSQEEMTKNQVSLTCL

VKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSRLTVDKSRWQ

EGNVFSCSVMHEALHNHYTQKSLSLSLGK.

In some cases, the spacer has 1, 2, 3, 4, or 5 single amino acid changes (e.g., conservative changes) compared to SEQ ID NO:125. In some cases, the IgG4 Fc hinge/linker region

that is mutated at two positions (L235E; N297Q) in a manner that reduces binding by Fc receptors (FcRs).

[0037] Any flexible linker described herein can be a repeat of GGGS (SEQ ID NO:127). Any flexible linker can comprise one, two, three, four, five, or more repeats of SEQ ID NO:127. Any flexible linker can also have 1, 2, 3, 4 of 5 amino acid changes (preferably conservative) compared to the repeats of SEQ ID NO:127.

[0038] A variety of transmembrane domains can be used in any CAR or polypeptide described herein. Table 3 includes examples of suitable transmembrane domains. Where a spacer region is present, the transmembrane domain (TM) is located carboxy terminal to the spacer region.

TABLE 3

Examples of Transmembrane Domains

Name	Accession	Length	Sequence
CD3z	J04132.1	21 aa	LCYLLDGILFIYGVILTALFL (SEQ ID NO: 128)
CD28	NM_006139	27 aa	FWVLVVVGGVLACYSLLVTVAF IIFWV (SEQ ID NO: 129)
CD28(M)	NM_006139	28 aa	MFWVLVVVGGVLACYSLLVTVA FIIFWV (SEQ ID NO: 130)
CD4	M35160	22 aa	MALIVLGGVAGLLLFIGLGIFF (SEQ ID NO: 131)
CD8tm	NM_001768	21 aa	IYIWAPLAGTCGVLLLSLVIT (SEQ ID NO: 132)
CD8tm2	NM_001768	23 aa	IYIWAPLAGTCGVLLLSLVITLY (SEQ ID NO: 133)
CD8tm3	NM_001768	24 aa	IYIWAPLAGTCGVLLLSLVITLY C (SEQ ID NO: 134)
41BB	NM_001561	27 aa	IISFFLALTSTALLFLLFF LTLRFSVV (SEQ ID NO: 135)
NKG2D	NM_007360	21 aa	PFFFCCFIAVAMGIRFIIMVA (SEQ ID NO: 136)

[0039] A costimulatory domain in any CAR or polypeptide described herein can be any domain that is suitable for use with a CD3ζ signaling domain. In some cases the co-signaling domain is a 4-1BB co-signaling domain that includes a sequence that is at least 90%, at least 95%, at least 98% identical to or identical to:

(SEQ ID NO: 140)
KRGRKKLLYIFKQPFMRPVQTTQEEDGCSCRFPEEEEGGCEL.

In some cases, the 4-1BB co-signaling domain has 1, 2, 3, 4 of 5 amino acid changes (preferably conservative) compared to SEQ TD NO:24.

[0040] The costimulatory domain(s) are located between the transmembrane domain and the CD3ζ signaling domain. Table 4 includes examples of suitable costimulatory domains together with the sequence of the CD3ζ signaling domain.

TABLE 4

CD35 Domain and Examples of Costimulatory Domains

Name	Accession	Length	Sequence
CD3ζ	J04132.1	113 aa	RVKFSRSADAPAYQQG QNQLYNELNLGRREEY DVLDKRRGRDPEMGGK PRRKNPQEGLYNELQK DKMAEAYSEIGMKGER RRGKGHDGLYQGLSTA TKDTYDALHMQALPPR (SEQ ID NO: 137)
CD28	NM_006139	42 aa	RSKRSRLLHSDYMNMT PRRPGPTRKHYQPYAP PRDFAAYRS (SEQ ID NO: 138)
CD28gg*	NM_006139	42 aa	RSKRSRGGHSDYMNMT PRRPGPTRKHYQPYAP PRDFAAYRS (SEQ ID NO: 139)
41BB	NM_001561	42 aa	KRGRKKLL YIFKQPFMRP VQTTQEEDGC SCRFPE EEEGGCEL (SEQ ID NO: 140)
OX40	NM_003327	42 aa	ALYLLRRDQRLPPDAHK PPGGGSFRTPIQEEQAD AHSTLAKI (SEQ ID NO: 141)
2B4	NM_016382	120 aa	WRRKRKEKQSETSPKEF LTIYEDVKDLKTRRNHE QEQTFPGGGSTIYSMIQ SQSSAPTSQEPAYTLYS LIQPSRKSGSRKRNHSP SFNSTIYEVIGKSQPK AQNPARLSRKELENFDV YS (SEQ ID NO: 142)

[0041] In various embodiments: the costimulatory domain is selected from the group consisting of: a costimulatory domain depicted in Table 4 or a variant thereof having 1-5 (e.g., 1 or 2) amino acid modifications, a CD28 costimulatory domain or a variant thereof having 1-5 (e.g., 1 or 2) amino acid modifications, a 4-1BB costimulatory domain or a variant thereof having 1-5 (e.g., 1 or 2) amino acid modifications and an OX40 costimulatory domain or a variant thereof having 1-5 (e.g., 1 or 2) amino acid modifications. In certain embodiments, a 4-1BB costimulatory domain or a variant thereof having 1-5 (e.g., 1 or 2) amino acid modifications in present. In some embodiments there are two costimulatory domains, for example a CD28 costimulatory domain or a variant thereof having 1-5 (e.g., 1 or 2) amino acid modifications (e.g., substitutions) and a 4-1BB co-stimulatory domain or a variant thereof having 1-5 (e.g., 1 or 2) amino acid modifications (e.g., substitutions). In various embodiments the 1-5 (e.g., 1 or 2) amino acid modification are substitutions. The costimulatory domain is amino terminal to the CD3ζ signaling domain and a short linker consisting of 2-10, e.g., 3 amino acids (e.g., GGG) is can be positioned between the costimulatory domain and the CD3ζ signaling domain.

[0042] Unless otherwise defined, all technical and scientific terms used herein have the same meaning as commonly understood by one of ordinary skill in the art to which this

invention belongs. Methods and materials are described herein for use in the present invention; other, suitable methods and materials known in the art can also be used. The materials, methods, and examples are illustrative only and not intended to be limiting. All publications, patent applications, patents, sequences, database entries, and other references mentioned herein are incorporated by reference in their entirety. In case of conflict, the present specification, including definitions, will control. All headings, sections, subheadings, and subsections are solely present for organization purposes and not meant to limit the scope therein. The content of each section can be applied to any and all aspects of the disclosure presented under any other heading, section, subheading, and subsection. Other features and advantages of the invention will be apparent from the following detailed description and figures, and from the claims.

DESCRIPTION OF THE DRAWINGS

[0043] FIG. **1**: Amino acid sequence of the CD6 CAR expressed by pF03496—CD6scFvop(VH_VL)-IgG4 (L235E,N297Q)op-CTLA4-Zetaop with the various domains marked. The mature CAR, lacking the signal sequence (MLLLVTSLLLCELPHPAFLLIP; SEQ ID NO:70) is SEQ ID NO:83. The immature sequence is SEQ ID NO:84.

[0044] FIG. **2**: Amino acid sequence of the CD6 CAR expressed by pF03497—CD6scFvop(VL_VH)-IgG4 (L235E,N297Q)op-CTLA4-Zetaop with the various domains marked. The mature CAR, lacking the signal sequence (MLLLVTSLLLCELPHPAFLLIP; SEQ ID NO:70) is SEQ ID NO:85. The immature sequence is SEQ ID NO:86.

[0045] FIG. **3**: Amino acid sequence of the CD6 CAR expressed by pF03488—CD6scFv(VH-VL)-IgG4op (L235E, N297Q)-41BB-Zetaop with the various domains marked. The mature CAR, lacking the signal sequence (MLLLVTSLLLCELPHPAFLLIP; SEQ ID NO:70) is SEQ ID NO:87. The immature sequence is SEQ ID NO:88.

[0046] FIG. **4**: Amino acid sequence of the CD6 CAR expressed by pF03491—CD6scFv(VL-VH)-IgG4op (L235E, N297Q)-41BB-Zetaop with the various domains marked. The mature CAR, lacking the signal sequence (MLLLVTSLLLCELPHPAFLLIP; SEQ ID NO:70) is SEQ ID NO:89. The immature sequence is SEQ ID NO:90.

[0047] FIG. **5**: Amino acid sequence of an alternative CD6 scFv for use in the CAR described herein (SEQ ID NO:73) the domains and mutations are indicated.

[0048] FIG. **6**A: schematic depictions of a representative CD6 CAR, a representative high affinity CD6 CAR, and a representative low affinity CD6 CAR, each with an IgG4 hinge, CD4TM, CTLA4 "co-stimulatory" domain, and CD3ζ. FIG. **6**B: schematic depictions of a representative CD6 CAR with a CTLA4 "co-stimulatory" domain, a representative CD6 CAR with an non-signaling CTLA4 "co-stimulatory" domain, and a representative CD19 CAR with a CTLA4 "co-stimulatory" domain, each also has an IgG4 hinge, CD4TM, and CD3ζ.

[0049] FIG. **7**: Depicts the results of a binding experiment showing the dissociation constant (KD) of the high affinity CD6 CAR, CD6 CAR, and low affinity CD6 CAR. Amino acid substitutions between the CD6, and high affinity CD6 CAR are also shown.

[0050] FIG. **8**: Is a schematic depiction of the preparation of Tregs. CD25+ cells are isolated from PBMC. FACS sorting is then used to enrich for CD4+/CD25high/CD127low/−. The resulting cells are highly enriched for Tregs. Optionally, an additional step can be used to enrich for the CD6low/− subset of Tregs.

[0051] FIG. **9**: Depicts the results of a study showing extracellular CD6 presence in Tregs expressing a CD6 CAR with either a 41BB or a CTLA4 signaling domain at 9 or 14 days post-induction.

[0052] FIG. **10**: Depicts the results of a study showing CD4+ presence in Tregs expressing a CD6 CAR with either a 41BB or a CTLA4 signaling domain at 14 days post-induction.

[0053] FIG. **11**: Depicts the results of a study showing cellular expansion of Tregs expressing either mock, a CD6 CAR with a 41BB signaling domain, or a CD6 CAR with CTLA4 signaling domain up to 14 days post-induction compared to Teff.

[0054] FIG. **12**: Depicts the results of a study showing CD6 or CTLA4 presence on Tregs expressing either mock, a CD6 CAR with a 41BB signaling domain, or a CD6 CAR with CTLA4 signaling domain 14 days post-induction compared to Teff and PBMC.

[0055] FIG. **13**: Depicts the results of a study showing unmethylated FOXP3 presence on Tregs expressing either mock, a CD6 CAR with a 41BB signaling domain, or a CD6 CAR with CTLA4 signaling domain 14 days post-induction compared to Teff and PBMC. Data were not multiplied by two as is done in some references.

[0056] FIG. **14**A: Is a schematic depiction of an experimental design to show antigen-specific stimulation of purified CD6 CAR Tregs. FIG. **14**B: Depicts the results of a study showing antigen-specific cell proliferation and cytokine expression of purified CD6 CAR Tregs or CD6 CAR Tregs with either a 41BB or a CTLA4 signaling domain.

[0057] FIG. **15**A: Is a schematic depiction of an experimental design to show use of CD6 CAR Tregs in treating lymphoproliferative disorders. FIG. **15**B: Depicts the results of a study showing CD6 expression the HuT78 cells. FIG. **15**C: Depicts the results of a study showing cell death of CD6-positive HuT78 cells as a result of treatment with CD6 CAR Tregs with either a 41BB or a CTLA4 signaling domain.

[0058] FIG. **16**A: Amino acid sequence of an optimized IL13 CAR: IL13op-IgG4op(L235E,N297Q)-CD4tmop-CTLA4-Zetaop-T2A-CD19t with the various domains marked is SEQ ID NO:91. FIG. **16**B: Amino acid sequence of a mature optimized IL13 CAR, lacking the signal sequence (MLLLVTSLLLCELPHPAFLLIP; SEQ ID NO:70)—IL13op-IgG4op(L235E,N297Q)-CD4tmop-CTLA4-Zetaop is SEQ ID NO:92.

[0059] FIG. **17**A: Amino acid sequence of an optimized CD6 CAR: CD6scFvop(VH-VL)-IgG4op(L235E,N297Q)-CD4tmop-41BB-Zetaop-T2A-CD19t with the various domains marked is SEQ ID NO:93. FIG. **17**B: Amino acid sequence of a mature optimized CD6 CAR, lacking the signal sequence (MLLLVTSLLLCELPHPAFLLIP; SEQ ID NO:70)—CD6scFvop(VH-VL)-IgG4op(L235E,N297Q)-CD4tmop-41BB-Zetaop is SEQ ID NO:94.

[0060] FIG. **18**A: Amino acid sequence of an optimized CD6 CAR: CD6scFvop(VH-VL)-IgG4op(L235E,N297Q)-CD4tmop-CLTA4-Zetaop-T2A-CD19t with the various domains marked is SEQ ID NO:95. FIG. **18**B: Amino acid sequence of a mature optimized IL13 CAR, lacking the signal sequence (MLLLVTSLLLCELPHPAFLLIP; SEQ ID

NO:70)—CD6scFvop(VH-VL)-IgG4op(L235E,N297Q)-CD4tmop-CTLA4-Zetaop is SEQ ID NO:96.

[0061] FIG. **19**A: Amino acid sequence of an optimized CD6 CAR: CD6scFvop(VH-VL)mhi-IgG4op(L235E, N297Q)-CD4tmop-41BB-Zetaop-T2A-CD19t with the various domains marked is SEQ ID NO:97. FIG. **19**B: Amino acid sequence of a mature optimized CD6 CAR, lacking the signal sequence (MLLLVTSLLLCELPHPAFLLIP; SEQ ID NO:70)—CD6scFvop(VH-VL)mhi-IgG4op(L235E, N297Q)-CD4tmop-41BB-Zetaop is SEQ ID NO:98.

[0062] FIG. **20**A: Amino acid sequence of an optimized CD6 CAR: CD6scFvop(VH-VL)mhi-IgG4op(L235E, N297Q)-CD4tmop-CLTA4-Zetaop-T2A-CD19t with the various domains marked is SEQ ID NO:99. FIG. **20**B: Amino acid sequence of a mature optimized CD6 CAR, lacking the signal sequence (MLLLVTSLLLCELPHPAFL-LIP; SEQ ID NO:70)—CD6scFvop(VH-VL)mhi-IgG4op (L235E,N297Q)-CD4tmop-CLTA4-Zetaop is SEQ ID NO:100.

[0063] FIG. **21**A: Amino acid sequence of an optimized CD19 CAR: CD19scFvop(VH-VL)-IgG4op(L235E, N297Q)-CD4tmop-CTLA4-Zetaop-T2A-EGFRt with the various domains marked is SEQ ID NO:114. FIG. **21**B: Amino acid sequence of a mature optimized CD19 CAR, lacking the signal sequence (MLLLVTSLLLCELPHPAFL-LIP; SEQ ID NO:70)—CD19scFvop(VH-VL)-IgG4op (L235E,N297Q)-CD4tmop-CTLA4-Zetaop is SEQ ID NO:115.

[0064] FIG. **22**A: A schematic depiction of a Treg expressing either a CD6scFvop(VH-VL) CAR with a 41BB domain or a CD6scFvop(VH-VL) CAR with a CTLA domain that can bind to a Teff expressing CD6 on its cell surface. FIG. **22**B: bar graphs showing measurement of various cytokine concentrations produced by Treg (first column on left; mock), Treg CAR^{41BB} (middle column), and Treg CAR^{CTLA} (third column) exposed to anti-CD6-Fc. FIG. **22**C: bar graphs showing the change of cytokine levels in percent (proinflammatory cytokines, cytokine release syndrome (CRS) cytokines, and anti-inflammatory cytokines) of Tregs versus Teff. For each cytokine measured, the far left (first) column is Treg (mock), the middle column is Treg CAR^{41BB}, and the third column is Treg CAR^{CTLA}. FIG. **22**D: box plot measurement of tumor cell count to show antigen-specific tumor killing by Tregs. FIG. **22**E: box plot measurement of the percent of CAR Treg needed to achieve the IC50 of Tregs (no CAR). IC50 here is the amount of Tregs required to suppress Teff proliferation by 50%.

[0065] FIG. **23**A: A schematic depiction of a Teff expressing either an IL-13 CAR with a 41BB domain or an IL-13 CAR with a CTLA domain that can bind to a tumor cell expressing an IL13R (IL13αR2 shown here) on its surface. FIG. **23**B: line graphs showing cellular expansion of Teffs (mock, IL13 CAR^{41BB} domain, or IL13 CAR^{CTLA4}) up to 14 days post-induction. FIG. **23**C: bar graphs showing cytokine concentration of Teffs in response to exposure to tumor cells. For each cytokine measured, the far left (first) column is Teff (mock), the middle column is Teff CAR^{41BB}, and the third column is Teff CAR^{CTLA}. FIG. **23**D: line graph showing antigen-specific cell lysis of tumor cells by Teff (mock), Teff CAR^{41BB}, and Teff CAR^{CTLA}.

[0066] FIG. **24**: A schematic depiction of the interaction between a CAR T cell of the disclosure, the mechanism of action, and enumerated advantages of each step.

DETAILED DESCRIPTION

[0067] Surprisingly, CARs with intermediate or low affinity slow, delay, or reduce the exhaustion of inoculated CAR-T cells, resulting in a longer half-life and improving efficacy for adoptive immunotherapy. In embodiments, compositions provided herein include CAR-T cells that target CD6+ T- and B-lymphocytes in the affected organs (e.g., pancreas in the case of T1D). In embodiments, the CARs provided herein have an affinity, e.g., a K_D of 30 nM or higher for the CD6 molecule (i.e., protein). The CAR-T cells provided herein are contemplated as relevant for the treatment of human autoimmune diseases (e.g., Type 1 Diabetes, Multiple Sclerosis, Inflammatory Bowel Disease, or Graft-versus-Host Disease). Also described herein is a method of treating can tumor or cancer that expresses a CD6 and/or an CD19 and/or an IL-13 receptor (e.g., IL-13Rα2): including, e.g., glioblastoma, primary brain tumors and gliomas (glioblastoma multiforme WHO Grade IV, anaplastic astrocytoma WHO Grade III, low-grade astrocytoma WHO Grade II, pilocytic astrocytoma WHO Grade I, other ungraded gliomas, oligodendroglioma, gliosarcoma, ganglioglioma, meningioma, ependymona), neuroectodermal tumors (medulloblastoma, neuroblastoma, ganglioneuroma, melanoma (metastatic), melanoma (primary), pheochromocytoma, Ewing's sarcoma, primitive neuroectodermal tumors, small cell lung carcinoma, Schwannoma), other brain tumors (epidermoid cysts, brain tumors of unknown pathology, pituitary gland of glioblastoma multiforme pt., metastatic tumors to brain of unknown tissue origin), melanoma, melanoma metastases, breast cancer, breast cancer metastases, kidney cancer, kidney cancer metastases, liver cancer, liver cancer metastases, lung cancer, lung cancer metastases, lymphoma, lymphoma metastases, ovarian cancer, ovarian cancer metastases, pancreatic cancer, pancreatic cancer metastases, prostate cancer, prostate cancer metastases, colorectal cancer, colorectal cancer metastases, combinations thereof, and the like, in a patient comprising administering a population of autologous or allogeneic human T cells transduced by a vector comprising a nucleic acid molecule described herein. In various embodiments: a chimeric antigen receptor described herein is administered locally or systemically; in some embodiments, a method of treatment includes cells expressing one or more of a CD6 receptor and/or an CD19 receptor and/or IL-13Rα2, and the cells are cancerous cells; and a chimeric antigen receptor described herein is administered by single or repeat dosing.

[0068] While various embodiments and aspects of the present invention are shown and described herein, it will be obvious to those skilled in the art that such embodiments and aspects are provided by way of example only. Numerous variations, changes, and substitutions will now occur to those skilled in the art without departing from the invention. It should be understood that various alternatives to the embodiments of the invention described herein may be employed in practicing the invention.

[0069] Unless defined otherwise, technical and scientific terms used herein have the same meaning as commonly understood by a person of ordinary skill in the art. See, e.g., Singleton et al., DICTIONARY OF MICROBIOLOGY AND MOLECULAR BIOLOGY 2nd ed., J. Wiley & Sons (New York, N.Y. 1994); Sambrook et al., MOLECULAR CLONING, A LABORATORY MANUAL, Cold Springs Harbor Press (Cold Springs Harbor, N Y 1989). Any methods, devices and materials similar or equivalent to those

described herein can be used in the practice of this invention. The following definitions are provided to facilitate understanding of certain terms used frequently herein and are not meant to limit the scope of the present disclosure. The abbreviations used herein have their conventional meaning within the chemical and biological arts. The section headings used herein are for organizational purposes only and are not to be construed as limiting the subject matter described. All documents, or portions of documents, cited in the application including, without limitation, patents, patent applications, articles, books, manuals, and treatises are hereby expressly incorporated by reference in their entirety for any purpose.

[0070] As used herein, the term "about" means a range of values including the specified value, which a person of ordinary skill in the art would consider reasonably similar to the specified value. In embodiments, the term "about" means within a standard deviation using measurements generally acceptable in the art. In embodiments, about means a range extending to +/−10% of the specified value. In embodiments, about means the specified value.

[0071] The terms "a" or "an," as used in herein means one or more.

[0072] The transitional term "comprising," which is synonymous with "including," "containing," or "characterized by," is inclusive or open-ended and does not exclude additional, unrecited elements (such as method steps or ingredients). By contrast, the transitional phrase "consisting of" excludes any element not specified in the claim. The transitional phrase "consisting essentially of" limits the scope of a claim to the specified materials or steps "and those that do not materially affect the basic and novel characteristic(s)" of the claimed invention. Where methods and compositions are disclosed using the transitional term "comprising" it will be understood that corresponding methods and compositions with the transitional term "consisting of" and "consisting essentially of" are also disclosed.

[0073] Where a parameter range is provided, all integers within that range, and tenths thereof, are also provided by the invention. For example, "0.2-5 mg" is a disclosure of 0.2 mg, 0.3 mg, 0.4 mg, 0.5 mg, 0.6 mg etc. up to and including 5.0 mg.

[0074] In the descriptions herein and in the claims, phrases such as "at least one of" or "one or more of" may occur followed by a conjunctive list of elements or features. The term "and/or" may also occur in a list of two or more elements or features. Unless otherwise implicitly or explicitly contradicted by the context in which it is used, such a phrase is intended to mean any of the listed elements or features individually or any of the recited elements or features in combination with any of the other recited elements or features. For example, the phrases "at least one of A and B;" "one or more of A and B;" and "A and/or B" are each intended to mean "A alone, B alone, or A and B together." A similar interpretation is also intended for lists including three or more items. For example, the phrases "at least one of A, B, and C;" "one or more of A, B, and C;" and "A, B, and/or C" are each intended to mean "A alone, B alone, C alone, A and B together, A and C together, B and C together, or A and B and C together."

[0075] "Nucleic acid" refers to deoxyribonucleotides or ribonucleotides and polymers thereof in either single- or double-stranded form, and complements thereof. The term "polynucleotide" refers to a linear sequence of nucleotides. The term "nucleotide" typically refers to a single unit of a polynucleotide, i.e., a monomer. Nucleotides can be ribonucleotides, deoxyribonucleotides, or modified versions thereof. Examples of polynucleotides contemplated herein include single and double stranded DNA, single and double stranded RNA (including siRNA), and hybrid molecules having mixtures of single and double stranded DNA and RNA. Nucleic acid as used herein also refers to nucleic acids that have the same basic chemical structure as a naturally occurring nucleic acid. Such analogues have modified sugars and/or modified ring substituents, but retain the same basic chemical structure as the naturally occurring nucleic acid. A nucleic acid mimetic refers to chemical compounds that have a structure that is different from the general chemical structure of a nucleic acid, but that functions in a manner similar to a naturally occurring nucleic acid. Examples of such analogues include, without limitation, phosphorothiolates, phosphoramidates, methyl phosphonates, chiral-methyl phosphonates, 2-O-methyl ribonucleotides, and peptide-nucleic acids (PNAs).

[0076] The term "amino acid" refers to naturally occurring and synthetic amino acids, as well as amino acid analogs and amino acid mimetics that function in a manner similar to the naturally occurring amino acids. Naturally occurring amino acids are those encoded by the genetic code, as well as those amino acids that are later modified, e.g., hydroxyproline, γ-carboxyglutamate, and O-phosphoserine. Amino acid analogs refers to compounds that have the same basic chemical structure as a naturally occurring amino acid, i.e., an a carbon that is bound to a hydrogen, a carboxyl group, an amino group, and an R group, e.g., homoserine, norleucine, methionine sulfoxide, methionine methyl sulfonium. Such analogs have modified R groups (e.g., norleucine) or modified peptide backbones, but retain the same basic chemical structure as a naturally occurring amino acid. Amino acid mimetics refers to chemical compounds that have a structure that is different from the general chemical structure of an amino acid, but that function in a manner similar to a naturally occurring amino acid.

[0077] Amino acids may be referred to herein by either their commonly known three letter symbols or by the one-letter symbols recommended by the IUPAC-IUB Biochemical Nomenclature Commission. Nucleotides, likewise, may be referred to by their commonly accepted single-letter codes.

[0078] The term "isolated", when applied to a nucleic acid or protein, denotes that the nucleic acid or protein is essentially free of other cellular components with which it is associated in the natural state. It can be, for example, in a homogeneous state and may be in either a dry or aqueous solution. Purity and homogeneity are typically determined using analytical chemistry techniques such as polyacrylamide gel electrophoresis or high performance liquid chromatography. A protein that is the predominant species present in a preparation is substantially purified.

[0079] "Conservatively modified variants" applies to both amino acid and nucleic acid sequences. With respect to particular nucleic acid sequences, conservatively modified variants refers to those nucleic acids which encode identical or essentially identical amino acid sequences, or where the nucleic acid does not encode an amino acid sequence, to essentially identical sequences. Because of the degeneracy of the genetic code, a large number of functionally identical nucleic acids sequences encode any given amino acid resi-

due. For instance, the codons GCA, GCC, GCG and GCU all encode the amino acid alanine. Thus, at every position where an alanine is specified by a codon, the codon can be altered to any of the corresponding codons described without altering the encoded polypeptide. Such nucleic acid variations are "silent variations," which are one species of conservatively modified variations. Every nucleic acid sequence herein which encodes a polypeptide also describes every possible silent variation of the nucleic acid. One of skill will recognize that each codon in a nucleic acid (except AUG, which is ordinarily the only codon for methionine, and TGG, which is ordinarily the only codon for tryptophan) can be modified to yield a functionally identical molecule. Accordingly, each silent variation of a nucleic acid which encodes a polypeptide is implicit in each described sequence with respect to the expression product, but not with respect to actual probe sequences.

[0080] As to amino acid sequences, one of skill will recognize that individual substitutions, deletions or additions to a nucleic acid, peptide, polypeptide, or protein sequence which alters, adds or deletes a single amino acid or a small percentage of amino acids in the encoded sequence is a "conservatively modified variant." In embodiments, the alteration results in the substitution of an amino acid with a chemically similar amino acid. Conservative substitution tables providing functionally similar amino acids are well known in the art. Such conservatively modified variants are in addition to and do not exclude polymorphic variants, interspecies homologs, and alleles of the invention.

[0081] The following eight groups each contain amino acids that are conservative substitutions for one another: 1) Alanine (A), Glycine (G); 2) Aspartic acid (D), Glutamic acid (E); 3) Asparagine (N), Glutamine (Q); 4) Arginine (R), Lysine (K); 5) Isoleucine (I), Leucine (L), Methionine (M), Valine (V); 6) Phenylalanine (F), Tyrosine (Y), Tryptophan (W); 7) Serine (S), Threonine (T); and 8) Cysteine (C), Methionine (M) (see, e.g., Creighton, Proteins (1984)).

[0082] An amino acid or nucleotide base "position" is denoted by a number that sequentially identifies each amino acid (or nucleotide base) in the reference sequence based on its position relative to the N-terminus (or 5'-end). Due to deletions, insertions, truncations, fusions, and the like that may be taken into account when determining an optimal alignment, in general the amino acid residue number in a test sequence determined by simply counting from the N-terminus will not necessarily be the same as the number of its corresponding position in the reference sequence. For example, in a case where a variant has a deletion relative to an aligned reference sequence, there will be no amino acid in the variant that corresponds to a position in the reference sequence at the site of deletion. Where there is an insertion in an aligned reference sequence, that insertion will not correspond to a numbered amino acid position in the reference sequence. In the case of truncations or fusions there can be stretches of amino acids in either the reference or aligned sequence that do not correspond to any amino acid in the corresponding sequence.

[0083] The terms "numbered with reference to" or "corresponding to," when used in the context of the numbering of a given amino acid or polynucleotide sequence, refers to the numbering of the residues of a specified reference sequence when the given amino acid or polynucleotide sequence is compared to the reference sequence. An amino acid residue in a protein "corresponds" to a given residue when it occupies the same essential structural position within the protein as the given residue. For example, a selected residue in a selected antibody (or antigen binding domain) corresponds to light chain threonine at Kabat position 40, when the selected residue occupies the same essential spatial or other structural relationship as a light chain threonine at Kabat position 40. In some embodiments, where a selected protein is aligned for maximum homology with the light chain of an antibody (or antigen binding domain), the position in the aligned selected protein aligning with threonine 40 is said to correspond to threonine 40. Instead of a primary sequence alignment, a three dimensional structural alignment can also be used, e.g., where the structure of the selected protein is aligned for maximum correspondence with the light chain threonine at Kabat position 40, and the overall structures compared. In this case, an amino acid that occupies the same essential position as threonine 40 in the structural model is said to correspond to the threonine 40 residue.

[0084] "Percentage of sequence identity" is determined by comparing two optimally aligned sequences over a comparison window, wherein the portion of the polynucleotide or polypeptide sequence in the comparison window may comprise additions or deletions (i.e., gaps) as compared to the reference sequence (which does not comprise additions or deletions) for optimal alignment of the two sequences. The percentage is calculated by determining the number of positions at which the identical nucleic acid base or amino acid residue occurs in both sequences to yield the number of matched positions, dividing the number of matched positions by the total number of positions in the window of comparison and multiplying the result by 100 to yield the percentage of sequence identity.

[0085] The terms "identical" or percent "identity," in the context of two or more nucleic acids or polypeptide sequences, refer to two or more sequences or subsequences that are the same or have a specified percentage of amino acid residues or nucleotides that are the same (i.e., 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, 98%, or 99% identity over a specified region, e.g., of the entire polypeptide sequences of the invention or individual domains of the polypeptides of the invention), when compared and aligned for maximum correspondence over a comparison window, or designated region as measured using a sequence comparison algorithms or by manual alignment and visual inspection. Such sequences that are at least about 80% identical are said to be "substantially identical." In some embodiments, two sequences are 100% identical. In certain embodiments, two sequences are 100% identical over the entire length of one of the sequences (e.g., the shorter of the two sequences where the sequences have different lengths). In various embodiments, identity may refer to the complement of a test sequence. In some embodiments, the identity exists over a region that is at least about 10 to about 100, about 20 to about 75, about 30 to about 50 amino acids or nucleotides in length. In certain embodiments, the identity exists over a region that is at about 10 nucleotides in length, or more preferably over a region that is 20 to 50, 100 to 500 or 1000 or more nucleotides in length. In certain embodiments, the identity exists over a region that is at least about 50 amino acids in length, or more preferably over a region that is 100 to 500, 100 to 200, 150 to 200, 175 to 200, 175 to 225, 175 to 250, 200 to 225, 200 to 250 or more amino acids in length.

[0086] For sequence comparison, typically one sequence acts as a reference sequence, to which test sequences are compared. When using a sequence comparison algorithm, test and reference sequences are entered into a computer, subsequence coordinates are designated, if necessary, and sequence algorithm program parameters are designated. Preferably, default program parameters can be used, or alternative parameters can be designated. The sequence comparison algorithm then calculates the percent sequence identities for the test sequences relative to the reference sequence, based on the program parameters.

[0087] A "comparison window" refers to a segment of any one of the number of contiguous positions (e.g., least about 10 to about 100, about 20 to about 75, about 30 to about 50, 100 to 500, 100 to 200, 150 to 200, 175 to 200, 175 to 225, 175 to 250, 200 to 225, 200 to 250) in which a sequence may be compared to a reference sequence of the same number of contiguous positions after the two sequences are optimally aligned. In various embodiments, a comparison window is the entire length of one or both of two aligned sequences. In some embodiments, two sequences being compared comprise different lengths, and the comparison window is the entire length of the longer or the shorter of the two sequences. In certain embodiments relating to two sequences of different lengths, the comparison window includes the entire length of the shorter of the two sequences. In some embodiments relating to two sequences of different lengths, the comparison window includes the entire length of the longer of the two sequences.

[0088] Methods of alignment of sequences for comparison are well known in the art. Optimal alignment of sequences for comparison can be conducted, e.g., by the local homology algorithm of Smith and Waterman (1970) Adv. Appl. Math. 2:482c, by the homology alignment algorithm of Needleman and Wunsch (1970) J. Mol. Biol. 48:443, by the search for similarity method of Pearson and Lipman (1988) Proc. Nat'l. Acad. Sci. USA 85:2444, by computerized implementations of these algorithms (GAP, BESTFIT, FASTA, and TFASTA in the Wisconsin Genetics Software Package, Genetics Computer Group, 575 Science Dr., Madison, Wis.), or by manual alignment and visual inspection (see, e.g., Ausubel et al., Current Protocols in Molecular Biology (1995 supplement)).

[0089] Examples of algorithm that are suitable for determining percent sequence identity and sequence similarity are the BLAST and BLAST 2.0 algorithms, which are described in Altschul et al. (1977) *Nuc. Acids Res.* 25:3389-3402, and Altschul et al. (1990) *J. Mol. Biol.* 215:403-410, respectively. BLAST and BLAST 2.0 may be used, with the parameters described herein, to determine percent sequence identity for nucleic acids and proteins. Software for performing BLAST analyses is publicly available through the National Center for Biotechnology Information (NCBI), as is known in the art. Software for performing BLAST analyses is publicly available through the National Center for Biotechnology Information (ncbi.nlm.nih.gov/). This algorithm involves first identifying high scoring sequence pairs (HSPs) by identifying short words of length W in the query sequence, which either match or satisfy some positive-valued threshold score T when aligned with a word of the same length in a database sequence. T is referred to as the neighborhood word score threshold (Altschul et al., supra). These initial neighborhood word hits act as seeds for initiating searches to find longer HSPs containing them. The word hits are extended in both directions along each sequence for as far as the cumulative alignment score can be increased. Cumulative scores are calculated using, for nucleotide sequences, the parameters M (reward score for a pair of matching residues; always >0) and N (penalty score for mismatching residues; always <0). For amino acid sequences, a scoring matrix is used to calculate the cumulative score. Extension of the word hits in each direction are halted when: the cumulative alignment score falls off by the quantity X from its maximum achieved value; the cumulative score goes to zero or below, due to the accumulation of one or more negative-scoring residue alignments; or the end of either sequence is reached. The BLAST algorithm parameters W, T, and X determine the sensitivity and speed of the alignment. In certain embodiments, the NCBI BLASTN or BLASTP program is used to align sequences. In certain embodiments, the BLASTN or BLASTP program uses the defaults used by the NCBI. In certain embodiments, the BLASTN program (for nucleotide sequences) uses as defaults: a word size (W) of 28; an expectation threshold (E) of 10; max matches in a query range set to 0; match/mismatch scores of 1,−2; linear gap costs; the filter for low complexity regions used; and mask for lookup table only used. In certain embodiments, the BLASTP program (for amino acid sequences) uses as defaults: a word size (W) of 3; an expectation threshold (E) of 10; max matches in a query range set to 0; the BLOSUM62 matrix (see Henikoff & Henikoff, Proc. Natl. Acad. Sci. USA 89:10915 (1992)); gap costs of existence: 11 and extension: 1; and conditional compositional score matrix adjustment.

[0090] The BLAST algorithm also performs a statistical analysis of the similarity between two sequences (see, e.g., Karlin and Altschul (1993) *Proc. Natl. Acad. Sci. USA* 90:5873-5787). One measure of similarity provided by the BLAST algorithm is the smallest sum probability (P(N)), which provides an indication of the probability by which a match between two nucleotide or amino acid sequences would occur by chance. For example, a nucleic acid is considered similar to a reference sequence if the smallest sum probability in a comparison of the test nucleic acid to the reference nucleic acid is less than about 0.2, more preferably less than about 0.01, and most preferably less than about 0.001.

[0091] In certain embodiments, an indication that two nucleic acid sequences or polypeptides are substantially identical is that the polypeptide encoded by the first nucleic acid is immunologically cross-reactive with the antibodies raised against the polypeptide encoded by the second nucleic acid, as described below. Thus, a polypeptide is typically substantially identical to a second polypeptide, for example, where the two peptides differ only by conservative substitutions. Another indication that two nucleic acid sequences are substantially identical is that the two molecules or their complements hybridize to each other under stringent conditions, as described below. Yet another indication that two nucleic acid sequences are substantially identical is that the same primers can be used to amplify the sequence.

[0092] The terms "polypeptide," "peptide" and "protein" are used interchangeably herein to refer to a polymer of amino acid residues, wherein the polymer may optionally be conjugated to a moiety that does not consist of amino acids. The terms apply to amino acid polymers in which one or more amino acid residue is an artificial chemical mimetic of a corresponding naturally occurring amino acid, as well as

to naturally occurring amino acid polymers and non-naturally occurring amino acid polymers. A "fusion protein" refers to a chimeric protein encoding two or more separate protein sequences that are recombinantly expressed as a single moiety.

[0093] A "label" or a "detectable moiety" is a composition detectable by spectroscopic, photochemical, biochemical, immunochemical, chemical, or other physical means. For example, useful labels include ^{32}P, fluorescent dyes, electron-dense reagents, enzymes (e.g., as commonly used in an ELISA), biotin, digoxigenin, or haptens and proteins or other entities which can be made detectable, e.g., by incorporating a radiolabel into a peptide or antibody specifically reactive with a target peptide. Any appropriate method known in the art for conjugating an antibody to the label may be employed, e.g., using methods described in Hermanson, Bioconjugate Techniques 1996, Academic Press, Inc., San Diego.

[0094] A "labeled protein or polypeptide" is one that is bound, either covalently, through a linker or a chemical bond, or noncovalently, through ionic, van der Waals, electrostatic, or hydrogen bonds to a label such that the presence of the labeled protein or polypeptide may be detected by detecting the presence of the label bound to the labeled protein or polypeptide. Alternatively, methods using high affinity interactions may achieve the same results where one of a pair of binding partners binds to the other, e.g., biotin, streptavidin.

[0095] "Antibody" refers to a polypeptide comprising a framework region from an immunoglobulin gene or fragments thereof that specifically binds and recognizes an antigen. The recognized immunoglobulin genes include the kappa, lambda, alpha, gamma, delta, epsilon, and mu constant region genes, as well as the myriad immunoglobulin variable region genes. Light chains are classified as either kappa or lambda. Heavy chains are classified as gamma, mu, alpha, delta, or epsilon, which in turn define the immunoglobulin classes, IgG, IgM, IgA, IgD and IgE, respectively. Typically, the antigen-binding region of an antibody plays a significant role in determining the specificity and affinity of binding. In some embodiments, antibodies or fragments of antibodies may be derived from different organisms, including humans, mice, rats, hamsters, camels, etc. Antibodies of the invention may include antibodies that have been modified or mutated at one or more amino acid positions to improve or modulate a desired function of the antibody (e.g. glycosylation, expression, antigen recognition, effector functions, antigen binding, specificity, etc.).

[0096] Antibodies are large, complex molecules (molecular weight of ~150,000 or about 1320 amino acids) with intricate internal structure. A natural antibody molecule contains two identical pairs of polypeptide chains, each pair having one light chain and one heavy chain. Each light chain and heavy chain in turn consists of two regions: a variable ("V") region involved in binding the target antigen, and a constant ("C") region that interacts with other components of the immune system. The light and heavy chain variable regions come together in 3-dimensional space to form a variable region that binds the antigen (for example, a receptor on the surface of a cell). Within each light or heavy chain variable region, there are three short segments (averaging 10 amino acids in length) called the complementarity determining regions ("CDRs"). The six CDRs in an antibody variable domain (three from the light chain and three from the heavy chain) fold up together in 3-dimensional space to form the actual antibody binding site which docks onto the target antigen. The position and length of the CDRs have been precisely defined by Kabat, E. et al., Sequences of Proteins of Immunological Interest, U.S. Department of Health and Human Services, 1983, 1987. The part of a variable region not contained in the CDRs is called the framework ("FR"), which forms the environment for the CDRs.

[0097] An exemplary immunoglobulin (antibody) structural unit comprises a tetramer. Each tetramer is composed of two identical pairs of polypeptide chains, each pair having one "light" (about 25 kD) and one "heavy" chain (about 50-70 kD). The N-terminus of each chain defines a variable region of about 100 to 110 or more amino acids primarily responsible for antigen recognition. The terms variable light chain (VL) and variable heavy chain (VH) refer to these light and heavy chains respectively. The Fc (i.e. fragment crystallizable region) is the "base" or "tail" of an immunoglobulin and is typically composed of two heavy chains that contribute two or three constant domains depending on the class of the antibody. By binding to specific proteins the Fc region ensures that each antibody generates an appropriate immune response for a given antigen. The Fc region also binds to various cell receptors, such as Fc receptors, and other immune molecules, such as complement proteins.

[0098] The term "antigen" as provided herein refers to molecules capable of binding to the antibody binding site.

[0099] Antibodies exist, for example, as intact immunoglobulins or as a number of well-characterized fragments produced by digestion with various peptidases. Thus, for example, pepsin digests an antibody below the disulfide linkages in the hinge region to produce F(ab)'2, a dimer of Fab which itself is a light chain joined to VH-CH1 by a disulfide bond. The F(ab)'2 may be reduced under mild conditions to break the disulfide linkage in the hinge region, thereby converting the F(ab)'2 dimer into an Fab' monomer. The Fab' monomer is essentially the antigen binding portion with part of the hinge region (see Fundamental Immunology (Paul ed., 3d ed. 1993). While various antibody fragments are defined in terms of the digestion of an intact antibody, one of skill will appreciate that such fragments may be synthesized de novo either chemically or by using recombinant DNA methodology. Thus, the term antibody, as used herein, also includes antibody fragments either produced by the modification of whole antibodies, or those synthesized de novo using recombinant DNA methodologies (e.g., single chain Fv) or those identified using phage display libraries (see, e.g., McCafferty et al., Nature 348:552-554 (1990)).

[0100] A single-chain variable fragment (scFv) is typically a fusion protein of the variable regions of the heavy (VH) and light chains (VL) of immunoglobulins, connected with a linker peptide (e.g., a short linker peptide of 10 to about 25 amino acids). In embodiments, the linker is rich in glycine for flexibility, as well as serine or threonine for solubility. The linker can either connect the N-terminus of the VH with the C-terminus of the VL, or vice versa.

[0101] The epitope of a mAb is the region of its antigen to which the mAb binds. Two antibodies bind to the same or overlapping epitope if each competitively inhibits (blocks) binding of the other to the antigen. That is, a 1×, 5×, 10×, 20× or 100× excess of one antibody inhibits binding of the other by at least 30% but preferably 50%, 75%, 90% or even 99% as measured in a competitive binding assay (see, e.g., Junghans et al., Cancer Res. 50:1495, 1990). Alternatively,

two antibodies have the same epitope if essentially all amino acid mutations in the antigen that reduce or eliminate binding of one antibody reduce or eliminate binding of the other. Two antibodies have overlapping epitopes if some amino acid mutations that reduce or eliminate binding of one antibody reduce or eliminate binding of the other.

[0102] For preparation of suitable antibodies, many techniques known in the art can be used (see, e.g., Kohler & Milstein, Nature 256:495-497 (1975); Kozbor et al., Immunology Today 4: 72 (1983); Cole et al., pp. 77-96 in Monoclonal Antibodies and Cancer Therapy, Alan R. Liss, Inc. (1985); Coligan, Current Protocols in Immunology (1991); Harlow & Lane, Antibodies, A Laboratory Manual (1988); and Goding, Monoclonal Antibodies: Principles and Practice (2d ed. 1986)). The genes encoding the heavy and light chains of an antibody of interest can be cloned from a cell, e.g., the genes encoding a monoclonal antibody can be cloned from a hybridoma and used to produce a recombinant monoclonal antibody. Gene libraries encoding heavy and light chains of monoclonal antibodies can also be made from hybridoma or plasma cells. Random combinations of the heavy and light chain gene products generate a large pool of antibodies with different antigenic specificity (see, e.g., Kuby, Immunology (3rd ed. 1997)). Techniques for the production of single chain antibodies or recombinant antibodies (U.S. Pat. Nos. 4,946,778, 4,816,567) can be adapted to produce antibodies to polypeptides of this invention. Also, transgenic mice, or other organisms such as other mammals, may be used to express humanized or human antibodies (see, e.g., U.S. Pat. Nos. 5,545,807; 5,545,806; 5,569,825; 5,625,126; 5,633,425; 5,661,016, Marks et al., Bio/Technology 10:779-783 (1992); Lonberg et al., Nature 368:856-859 (1994); Morrison, Nature 368:812-13 (1994); Fishwild et al., Nature Biotechnology 14:845-51 (1996); Neuberger, Nature Biotechnology 14:826 (1996); and Lonberg & Huszar, Intern. Rev. Immunol. 13:65-93 (1995)). Alternatively, phage display technology can be used to identify antibodies and heteromeric Fab fragments that specifically bind to selected antigens (see, e.g., McCafferty et al., Nature 348:552-554 (1990); Marks et al., Biotechnology 10:779-783 (1992)). Antibodies can also be made bispecific, i.e., able to recognize two different antigens (see, e.g., WO 93/08829, Traunecker et al., EMBO J. 10:3655-3659 (1991); and Suresh et al., Methods in Enzymology 121:210 (1986)). Antibodies can also be heteroconjugates, e.g., two covalently joined antibodies, or immunotoxins (see, e.g., U.S. Pat. No. 4,676,980, WO 91/00360; WO 92/200373; and EP 03089).

[0103] Methods for humanizing or primatizing non-human antibodies or scFvs are well known in the art (e.g., U.S. Pat. Nos. 4,816,567; 5,530,101; 5,859,205; 5,585,089; 5,693,761; 5,693,762; 5,777,085; 6,180,370; 6,210,671; and 6,329,511; WO 87/02671; EP Patent Application 0173494; Jones et al. (1986) Nature 321:522; and Verhoyen et al. (1988) Science 239:1534). Humanized antibodies are further described in, e.g., Winter and Milstein (1991) Nature 349:293. Generally, a humanized antibody has one or more amino acid residues introduced into it from a source which is non-human. These non-human amino acid residues are often referred to as import residues, which are typically taken from an import variable domain. Humanization can be essentially performed following the method of Winter and co-workers (see, e.g., Morrison et al., PNAS USA, 81:6851-6855 (1984), Jones et al., Nature 321:522-525 (1986); Riechmann et al., Nature 332:323-327 (1988); Morrison and Oi, Adv. Immunol., 44:65-92 (1988), Verhoeyen et al., Science 239:1534-1536 (1988) and Presta, Curr. Op. Struct. Biol. 2:593-596 (1992), Padlan, Molec. Immun., 28:489-498 (1991); Padlan, Molec. Immun., 31(3):169-217 (1994)), by substituting rodent CDRs or CDR sequences for the corresponding sequences of a human antibody. Accordingly, such humanized antibodies are chimeric antibodies (U.S. Pat. No. 4,816,567), wherein substantially less than an intact human variable domain has been substituted by the corresponding sequence from a non-human species. In practice, humanized antibodies are typically human antibodies in which some CDR residues and possibly some FR residues are substituted by residues from analogous sites in rodent antibodies. For example, polynucleotides comprising a first sequence coding for humanized immunoglobulin framework regions and a second sequence set coding for the desired immunoglobulin complementarity determining regions can be produced synthetically or by combining appropriate cDNA and genomic DNA segments. Human constant region DNA sequences can be isolated in accordance with well known procedures from a variety of human cells.

[0104] A "chimeric antibody" is an antibody molecule in which (a) the constant region, or a portion thereof, is altered, replaced or exchanged so that the antigen binding site (variable region) is linked to a constant region of a different or altered class, effector function and/or species, or an entirely different molecule which confers new properties to the chimeric antibody, e.g., an enzyme, toxin, hormone, growth factor, drug, etc.; or (b) the variable region, or a portion thereof, is altered, replaced or exchanged with a variable region having a different or altered antigen specificity. The preferred antibodies of, and for use according to the invention include humanized and/or chimeric monoclonal antibodies.

[0105] A "therapeutic antibody" as provided herein refers to any antibody or functional fragment thereof that is used to treat cancer, autoimmune diseases, transplant rejection, cardiovascular disease or other diseases or conditions such as those described herein.

[0106] Techniques for conjugating therapeutic agents to antibodies are well known (see, e.g., Arnon et al., "Monoclonal Antibodies For Immunotargeting Of Drugs In Cancer Therapy", in Monoclonal Antibodies And Cancer Therapy, Reisfeld et al. (eds.), pp. 243-56 (Alan R. Liss, Inc. 1985); Hellstrom et al., "Antibodies For Drug Delivery" in Controlled Drug Delivery (2^{nd} Ed.), Robinson et al. (eds.), pp. 623-53 (Marcel Dekker, Inc. 1987); Thorpe, "Antibody Carriers Of Cytotoxic Agents In Cancer Therapy: A Review" in Monoclonal Antibodies '84: Biological And Clinical Applications, Pinchera et al. (eds.), pp. 475-506 (1985); and Thorpe et al., "The Preparation And Cytotoxic Properties Of Antibody-Toxin Conjugates", Immunol. Rev., 62:119-58 (1982)). As used herein, the term "antibody-drug conjugate" or "ADC" refers to a therapeutic agent conjugated or otherwise covalently bound to an antibody. A "therapeutic agent" as referred to herein, is a composition useful in treating or preventing a disease such as an autoimmune disease.

[0107] The term "anti-CD6 antibody" as used herein refers to an antibody capable of binding CD6 through the antibody CDR sequences. Thus, the anti-CD6 antibody includes an antibody binding site composed of CDRs CDRs (e.g., VL-

CDR1, VL-CDR2, VL-CDR3, VH-CDR1, VH-CDR2, VH-CDR3) that specifically bind CD6

[0108] "CD6", also known as TP120, as referred to herein includes any of the recombinant or naturally-occurring forms of cluster of differentiation 6 (CD6) protein or variants or homologs thereof that maintain CD6 activity (e.g. within at least 50%, 80%, 90%, 95%, 96%, 97%, 98%, 99% or 100% activity compared to CD6). In aspects, the variants or homologs have at least 90%, 95%, 96%, 97%, 98%, 99% or 100% amino acid sequence identity across the whole sequence or a portion of the sequence (e.g. a 50, 100, 150 or 200 continuous amino acid portion) compared to a naturally occurring CD6 protein. In some cases, the CD6 protein is substantially identical to the protein identified by the Uni-Prot reference number P30203 or a variant or homolog having substantial identity thereto. In some cases, CD6 is a human CD6 protein. In some cases, a variant or mutant of the CD6 protein includes no more than 5, 4, 3, 2, or 1 deletions compared to a naturally occurring CD6 protein. In some cases, a variant or mutant of the CD6 protein includes no more than 5, 4, 3, 2, or 1 insertions compared to the naturally-occurring CD6 protein. In some cases, a variant or mutant of the CD6 protein does not include deletions compared to the naturally occurring CD6 protein. In some cases, a variant or mutant of the CD6 protein does not include insertions compared to the naturally occurring CD6 protein. In some cases, a variant or mutant of the CD6 protein includes substitutions that are conservative substitutions compared to the naturally occurring CD6 protein. In some cases, CD6 is the protein identified by the NCBI sequence reference NP_006716.3 or an isoform or naturally occurring mutant or variant thereof. In some cases, CD6 is the protein as identified by the NCBI sequence reference NP_001241679.1 or an isoform or naturally occurring mutant or variant thereof. In some cases, CD6 is the protein as identified by the NCBI sequence reference NP_001241680.1 or an isoform or naturally occurring mutant or variant thereof. Non-limiting examples of human CD6 amino acid sequences available under NCBI sequence references are as follows:

NP_006716.3

(SEQ ID NO: 1)

MWLFFGITGLLTAALSGHPSPAPPDQLNTSSAESEL

WEPGERLPVRLTNGSSSCSGTVEVRLEASWEPACGA

LWDSRAAEAVCRALGCGGAEAASQLAPPTPELPPPP

AAGNTSVAANATLAGAPALLCSGAEWRLCEVVEHAC

RSDGRRARVTCAENRALRLVDGGGACAGRVEMLEHG

EWGSVCDDTWDLEDAHVVCRQLGCGWAVQALPGLHF

TPGRGPIHRDQVNCSGAEAYLWDCPGLPGQHYCGHK

EDAGAVCSEHQSWRLTGGADRCEGQVEVHFRGVWNT

VCDSEWYPSEAKVLCQSLGCGTAVERPKGLPHSLSG

RMYYSCNGEELTLSNCSWRFNNSNLCSQSLAARVLC

SASRSLHNLSTPEVPASVQTVTIESSVTVKIENKES

RELMLLIPSIVLGILLLGSLIFIAFILLRIKGKYAL

PVMVNHQHLPTTIPAGSNSYQPVPITIPKEVFMLPI

-continued

QVQAPPPEDSDSGSDSDYEHYDFSAQPPVALTTFYN

SQRHRVTDEEVQQSRFQMPPLEEGLEELHASHIPTA

NPGHCITDPPSLGPQYHPRSNSESSTSSGEDYCNSP

KSKLPPWNPQVFSSERSSFLEQPPNLELAGTQPAFS

AGPPADDSSSTSSGEWYQNFQPPPQPPSEEQFGCPG

SPSPQPDSTDNDDYDDISAA

NP_001241679.1

(SEQ ID NO: 2)

MWLFFGITGLLTAALSGHPSPAPPDQLNTSSAESEL

WEPGERLPVRLTNGSSSCSGTVEVRLEASWEPACGA

LWDSRAAEAVCRALGCGGAEAASQLAPPTPELPPPP

AAGNTSVAANATLAGAPALLCSGAEWRLCEVVEHAC

RSDGRRARVTCAENRALRLVDGGGACAGRVEMLEHG

EWGSVCDDTWDLEDAHVVCRQLGCGWAVQALPGLHF

TPGRGPIHRDQVNCSGAEAYLWDCPGLPGQHYCGHK

EDAGAVCSEHQSWRLTGGADRCEGQVEVHFRGVWNT

VCDSEWYPSEAKVLCQSLGCGTAVERPKGLPHSLSG

RMYYSCNGEELTLSNCSWRFNNSNLCSQSLAARVLC

SASRSLHNLSTPEVPASVQTVTIESSVTVKIENKES

RELMLLIPSIVLGILLLGSLIFIAFILLRIKGKYAL

PVMVNHQHLPTTIPAGSNSYQPVPITIPKEDSQRHR

VTDEEVQQSRFQMPPLEEGLEELHASHIPTANPGHC

NP_001241680.1

(SEQ ID NO: 3)

MWLFFGITGLLTAALSGHPSPAPPDQLNTSSAESEL

WEPGERLPVRLTNGSSSCSGTVEVRLEASWEPACGA

LWDSRAAEAVCRALGCGGAEAASQLAPPTPELPPPP

AAGNTSVAANATLAGAPALLCSGAEWRLCEVVEHAC

RSDGRRARVTCAENRALRLVDGGGACAGRVEMLEHG

EWGSVCDDTWDLEDAHVVCRQLGCGWAVQALPGLHF

TPGRGPIHRDQVNCSGAEAYLWDCPGLPGQHYCGHK

EDAGAVCSEHQSWRLTGGADRCEGQVEVHFRGVWNT

VCDSEWYPSEAKVLCQSLGCGTAVERPKGLPHSLSG

RMYYSCNGEELTLSNCSWRFNNSNLCSQSLAARVLC

SASRSLHNLSTPEVPASVQTVTIESSVTVKIENKES

RELMLLIPSIVLGILLLGSLIFIAFILLRIKGKYAL

PVMVNHQHLPTTIPAGSNSYQPVPITIPKEDSQRHR

VTDEEVQQSRFQMPPLEEGLEELHASHIPTANPGHC

-continued

ITDPPSLGPQYHPRSNSESSTSSGEDYCNSPKSKLP

PWNPQVFSSERSSFLEQPPNLELAGTQPAFSGSPSP

QPDSTDNDDYDDISAA

[0109] The term "CD28 transmembrane domain" as provided herein includes any of the recombinant or naturally-occurring forms of the transmembrane domain of CD28, or variants or homologs thereof that maintain CD28 transmembrane domain activity (e.g. within at least 50%, 80%, 90%, 95%, 96%, 97%, 98%, 99% or 100% activity compared to the CD28 transmembrane domain). In some cases, the variants or homologs have at least 90%, 95%, 96%, 97%, 98%, 99% or 100% amino acid sequence identity across the whole sequence or a portion of the sequence (e.g. a 50, 100, 150 or 200 continuous amino acid portion) compared to a naturally occurring CD28 transmembrane domain polypeptide. In some cases, the CD28 transmembrane domain is a human CD28 transmembrane domain protein. In some cases, a variant or mutant of the CD28 transmembrane domain protein includes no more than 5, 4, 3, 2, or 1 deletions compared to the naturally occurring CD28 transmembrane domain protein. In some cases, a variant or mutant of the CD28 transmembrane domain protein includes no more than 5, 4, 3, 2, or 1 insertions compared to the naturally occurring CD28 transmembrane domain protein. In some cases, a variant or mutant of the CD28 transmembrane domain protein does not include deletions compared to the naturally occurring CD28 transmembrane domain protein. In some cases, a variant or mutant of the CD28 transmembrane domain protein does not include insertions compared to the naturally occurring CD28 transmembrane domain protein. In some cases, a variant or mutant of the CD28 transmembrane domain protein includes substitutions that are conservative substitutions compared to the naturally occurring CD28 transmembrane domain protein. In some cases, the CD28 transmembrane domain includes all or a portion of the protein as identified by NCBI sequence reference NP_001230006.1, or an isoform or naturally occurring mutant or variant thereof. In some cases, the CD28 transmembrane domain includes all or a portions of the protein as identified by the NCBI sequence reference NP_001230007.1, or an isoform or naturally occurring mutant or variant thereof. In some cases, the CD28 transmembrane domain includes all or a portion of the protein as identified by the NCBI sequence reference NP_006130.1, or an isoform or naturally occurring mutant or variant thereof. In some cases, In some cases, the CD28 transmembrane domain amino acid sequence includes the sequence of RSKRSRGGHSDYMNMTPRRPGPTRKHYQPYAPPRDFAAYRS (SEQ ID NO:7). In some cases, In some cases, the CD28 transmembrane domain amino acid sequence is the sequence of SEQ ID NO:7. In some cases, the CD28 transmembrane domain amino acid sequence includes the sequence of RSKRSRLLHSDYMNMTPRRPGPTRKHYQPYAPPRDFAAYRS (SEQ ID NO:8). In some cases, the CD28 transmembrane domain amino acid sequence is the sequence of SEQ ID NO:8. Non-limiting examples of human CD28 amino acid sequences available under NCBI sequence references are as follows:

NP_001230006.1

(SEQ ID NO: 4)

MLRLLLALNLFPSIQVTGNKILVKQSPMLVAYDNAV

NLSWKHLCPSPLFPGPSKPFWVLVVVGGVLACYSLL

VTVAFIIFWVRSKRSRLLHSDYMNMTPRRPGPTRKH

YQPYAPPRDFAAYRS

NP_001230007.1

(SEQ ID NO: 5)

MLRLLLALNLFPSIQVTGKHLCPSPLFPGPSKPFWV

LVVVGGVLACYSLLVTVAFIIFWVRSKRSRLLHSDY

MNMTPRRPGPTRKHYQPYAPPRDFAAYRS

NP_006130.1

(SEQ ID NO: 6)

MLRLLLALNLFPSIQVTGNKILVKQSPMLVAYDNAV

NLSCKYSYNLFSREFRASLHKGLDSAVEVCVVYGNY

SQQLQVYSKTGFNCDGKLGNESVTFYLQNLYVNQTD

IYFCKIEVMYPPPYLDNEKSNGTIIHVKGKHLCPSP

LFPGPSKPFWVLVVVGGVLACYSLLVTVAFIIFWVR

SKRSRLLHSDYMNMTPRRPGPTRKHYQPYAPPRDFA

AYRS

[0110] In some cases, the CD28 transmembrane domain is encoded by all or a portion of the nucleic acid sequence identified by the NCBI sequence reference NM_001243077.1, or an isoform or naturally occurring mutant or variant thereof. In some cases, the CD28 transmembrane domain is encoded by all or a portion the nucleic acid sequence identified by the NCBI sequence reference NM_001243078.1, or an isoform or naturally occurring mutant or variant thereof. In some cases, the CD28 transmembrane domain is encoded by all of a portion of the nucleic acid sequence identified by the NCBI sequence reference NM_006139.3, or an isoform or naturally occurring mutant or variant thereof. In some cases, a variant or mutant of the CD28 transmembrane domain nucleic acid sequence includes no more than 5, 4, 3, 2, or 1 deletions compared to the naturally occurring CD28 transmembrane domain nucleic acid sequence. In some cases, a variant or mutant of the CD28 transmembrane domain nucleic acid sequence includes no more than 5, 4, 3, 2, or 1 insertions compared to the naturally occurring CD28 transmembrane domain nucleic acid sequence. In some cases, a variant or mutant of the CD28 transmembrane domain nucleic acid sequence does not include deletions compared to the naturally occurring CD28 transmembrane domain nucleic acid sequence. In some cases, a variant or mutant of the CD28 transmembrane domain nucleic acid sequence does not include insertions compared to the naturally occurring CD28 transmembrane domain nucleic acid sequence. In some cases, a variant or mutant of the CD28 transmembrane domain nucleic acid sequence includes substitutions that are conservative substitutions compared to the naturally occurring CD28 transmembrane domain nucleic acid sequence.

[0111] The term "CD4 transmembrane domain" as provided herein includes any of the recombinant or naturally-occurring forms of the transmembrane domain of CD4, or variants or homologs thereof that maintain CD4 transmem-

brane domain activity (e.g. within at least 50%, 80%, 90%, 95%, 96%, 97%, 98%, 99% or 100% activity compared to the CD4 transmembrane domain). In some aspects, the variants or homologs have at least 90%, 95%, 96%, 97%, 98%, 99% or 100% amino acid sequence identity across the whole sequence or a portion of the sequence (e.g. a 50, 100, 150 or 200 continuous amino acid portion) compared to a naturally occurring CD4 transmembrane domain polypeptide. In some cases, the CD4 transmembrane domain amino acid sequence includes the sequence of MALIVLGGVAGLLLFIGLGIFF (SEQ ID NO:23). In some cases, the CD4 transmembrane domain amino acid sequence is the sequence of SEQ ID NO:23. A non-limiting example of a nucleotide sequence that encodes the CD4 transmembrane domain is ATGGCCCTGATTGTGCTGGGGGGCGTCGCCGGCCTCCTGCTTTTCATTGGGCTAGGC ATCTTCTTC (SEQ ID NO:24). In some cases, the CD4 transmembrane domain is a human CD4 transmembrane domain protein. In some cases, a variant or mutant of the CD4 transmembrane domain protein includes no more than 5, 4, 3, 2, or 1 deletions compared to the naturally occurring CD4 transmembrane domain protein. In some cases, a variant or mutant of the CD4 transmembrane domain protein includes no more than 5, 4, 3, 2, or 1 insertions compared to the naturally occurring CD4 transmembrane domain protein. In some cases, a variant or mutant of the CD4 transmembrane domain protein does not include deletions compared to the naturally occurring CD4 transmembrane domain protein. In some cases, a variant or mutant of the CD4 transmembrane domain protein does not include insertions compared to the naturally occurring CD4 transmembrane domain protein. In some cases, a variant or mutant of the CD4 transmembrane domain protein includes substitutions that are conservative substitutions compared to the naturally occurring CD4 transmembrane domain protein. In some cases, the CD4 transmembrane domain includes all or a portion of the protein identified by the NCBI sequence reference NP_000607.1, or an isoform or naturally occurring mutant or variant thereof. In some cases, the CD4 transmembrane domain includes all or a portion of the protein identified by the NCBI sequence reference NP_001181943.1, or an isoform or naturally occurring mutant or variant thereof. In some cases, the CD4 transmembrane domain includes all or a portion of the protein identified by the NCBI sequence reference NP_001181944.1, or an isoform or naturally occurring mutant or variant thereof. In some cases, the CD4 transmembrane domain includes all or a portion of the protein identified by the NCBI sequence reference NP_001181945.1, or an isoform or naturally occurring mutant or variant thereof. In some cases, the CD4 transmembrane domain includes all or a portion of the protein identified by the NCBI sequence reference NP_001181946.1, or an isoform or naturally occurring mutant or variant thereof. Non-limiting examples of human CD4 amino acid sequences available under NCBI sequence references are as follows:

NP_000607.1

(SEQ ID NO: 9)

MNRGVPFRHLLLVLQLALLPAATQGKKVVLGKKGDT

VELTCTASQKKSIQFHWKNSNQIKILGNQGSFLTKG

PSKLNDRADSRRSLWDQGNFPLIIKNLKIEDSDTYI

-continued

CEVEDQKEEVQLLVFGLTANSDTHLLQGQSLTLTLE

SPPGSSPSVQCRSPRGKNIQGGKTLSVSQLELQDSG

TWTCTVLQNQKKVEFKIDIVVLAFQKASSIVYKKEG

EQVEFSFPLAFTVEKLTGSGELWWQAERASSSKSWI

TFDLKNKEVSVKRVTQDPKLQMGKKLPLHLTLPQAL

PQYAGSGNLTLALEAKTGKLHQEVNLVVMRATQLQK

NLTCEVWGPTSPKLMLSLKLENKEAKVSKREKAVWV

LNPEAGMWQCLLSDSGQVLLESNIKVLPTWSTPVQP

MALIVLGGVAGLLLFIGLGIFFCVRCRHRRRQAERM

SQIKRLLSEKKTCQCPHRFQKTCSPI

NP_001181943.1

(SEQ ID NO: 10)

MPTPLVHPHLPISSPRVSPFPPPAPQKASSIVYKKE

GEQVEFSFPLAFTVEKLTGSGELWWQAERASSSKSW

ITFDLKNKEVSVKRVTQDPKLQMGKKLPLHLTLPQA

LPQYAGSGNLTLALEAKTGKLHQEVNLVVMRATQLQ

KNLTCEVWGPTSPKLMLSLKLENKEAKVSKREKAVW

VLNPEAGMWQCLLSDSGQVLLESNIKVLPTWSTPVQ

PMALIVLGGVAGLLLFIGLGIFFCVRCRHRRRQAER

MSQIKRLLSEKKTCQCPHRFQKTCSPI

NP_001181944.1

(SEQ ID NO: 11)

MGKKLPLHLTLPQALPQYAGSGNLTLALEAKTGKLH

QEVNLVVMRATQLQKNLTCEVWGPTSPKLMLSLKLE

NKEAKVSKREKAVWVLNPEAGMWQCLLSDSGQVLLE

SNIKVLPTWSTPVQPMALIVLGGVAGLLLFIGLGIF

FCVRCRHRRRQAERMSQIKRLLSEKKTCQCPHRFQK

TCSPI

NP_001181945.1

(SEQ ID NO: 12)

MGKKLPLHLTLPQALPQYAGSGNLTLALEAKTGKLH

QEVNLVVMRATQLQKNLTCEVWGPTSPKLMLSLKLE

NKEAKVSKREKAVWVLNPEAGMWQCLLSDSGQVLLE

SNIKVLPTWSTPVQPMALIVLGGVAGLLLFIGLGIF

FCVRCRHRRRQAERMSQIKRLLSEKKTCQCPHRFQK

TCSPI

NP_001181946.1

(SEQ ID NO: 13)

MGKKLPLHLTLPQALPQYAGSGNLTLALEAKTGKLH

QEVNLVVMRATQLQKNLTCEVWGPTSPKLMLSLKLE

NKEAKVSKREKAVWVLNPEAGMWQCLLSDSGQVLLE

-continued

SNIKVLPTWSTPVQPMALIVLGGVAGLLLFIGLGIF

FCVRCRHRRRQAERMSQIKRLLSEKKTCQCPHRFQK

TCSPI

[0112] In some cases, the CD4 transmembrane domain is encoded by all or a portion of the nucleic acid sequence identified by the NCBI sequence reference NM_000616.4, or an isoform or naturally occurring mutant or variant thereof. In some cases, the CD4 transmembrane domain is encoded by all or a portion of the nucleic acid sequence identified by the NCBI sequence reference NM_001195014.2, or an isoform or naturally occurring mutant or variant thereof. In some cases, the CD4 transmembrane domain is encoded by all or a portion of the nucleic acid sequence identified by the NCBI sequence reference NM_001195015.2, or an isoform or naturally occurring mutant or variant thereof. In some cases, the CD4 transmembrane domain is encoded by all or a portion of the nucleic acid sequence identified by the NCBI sequence reference NM_001195016.2, or an isoform or naturally occurring mutant or variant thereof. In some cases, the CD4 transmembrane domain is encoded by all or a portion of the nucleic acid sequence identified by the NCBI sequence reference NM_001195017.2, or an isoform or naturally occurring mutant or variant thereof. In some cases, a variant or mutant of the CD4 transmembrane domain nucleic acid sequence includes no more than 5, 4, 3, 2, or 1 deletions compared to the naturally occurring CD4 transmembrane domain nucleic acid sequence. In some cases, a variant or mutant of the CD4 transmembrane domain nucleic acid sequence includes no more than 5, 4, 3, 2, or 1 insertions compared to the naturally occurring CD4 transmembrane domain nucleic acid sequence. In some cases, a variant or mutant of the CD4 transmembrane domain nucleic acid sequence does not include deletions compared to the naturally occurring CD4 transmembrane domain nucleic acid sequence. In some cases, a variant or mutant of the CD4 transmembrane domain nucleic acid sequence does not include insertions compared to the naturally occurring CD4 transmembrane domain nucleic acid sequence. In some cases, a variant or mutant of the CD4 transmembrane domain nucleic acid sequence includes substitutions that are conservative substitutions compared to the naturally occurring CD4 transmembrane domain nucleic acid sequence.

[0113] The term "CD8 transmembrane domain" as provided herein includes any of the recombinant or naturally-occurring forms of the transmembrane domain of CD8, or variants or homologs thereof that maintain CD8 transmembrane domain activity (e.g. within at least 50%, 80%, 90%, 95%, 96%, 97%, 98%, 99% or 100% activity compared to the CD8 transmembrane domain). In some aspects, the variants or homologs have at least 90%, 95%, 96%, 97%, 98%, 99% or 100% amino acid sequence identity across the whole sequence or a portion of the sequence (e.g. a 50, 100, 150 or 200 continuous amino acid portion) compared to a naturally occurring CD8 transmembrane domain polypeptide. In some cases, the CD8 transmembrane domain amino acid sequence includes the sequence of IYIWAPLAGTCGVLLLSLVIT (SEQ ID NO:25). In some cases, the CD8 transmembrane domain amino acid sequence is the sequence of SEQ ID NO:25. In some cases, the CD8 transmembrane domain is CD8A transmembrane domain. In some cases, the CD8 transmembrane domain is a CD8B transmembrane domain. In some cases, the CD8 transmembrane domain is a human CD8 transmembrane domain protein. In some cases, a variant or mutant of the CD8 transmembrane domain protein includes no more than 5, 4, 3, 2, or 1 deletions compared to the naturally occurring CD8 transmembrane domain protein. In some cases, a variant or mutant of the CD8 transmembrane domain protein includes no more than 5, 4, 3, 2, or 1 insertions compared to the naturally occurring CD8 transmembrane domain protein. In some cases, a variant or mutant of the CD8 transmembrane domain protein does not include deletions compared to the naturally occurring CD8 transmembrane domain protein. In some cases, a variant or mutant of the CD8 transmembrane domain protein does not include insertions compared to the naturally occurring CD8 transmembrane domain protein. In some cases, a variant or mutant of the CD8 transmembrane domain protein includes substitutions that are conservative substitutions compared to the naturally occurring CD8 transmembrane domain protein. In some cases, the CD8 transmembrane domain includes all or a portion of the protein identified by the NCBI sequence reference NP_001139345.1, or an isoform or naturally occurring mutant or variant thereof. In some cases, the CD8 transmembrane domain includes all or a portion of the protein identified by the NCBI sequence reference NP_001181943.1, or an isoform or naturally occurring mutant or variant thereof. In some cases, the CD8 transmembrane domain includes all or a portion of the protein identified by the NCBI sequence reference NP_001181944.1, or an isoform or naturally occurring mutant or variant thereof. In some cases, the CD8 transmembrane domain includes all or a portion of the protein identified by the NCBI sequence reference NP_001181945.1, or an isoform or naturally occurring mutant or variant thereof. In some cases, the CD8 transmembrane domain includes all or a portion of the protein identified by the NCBI sequence reference NP_741969.1, or an isoform or naturally occurring mutant or variant thereof. In some cases, the CD8 transmembrane domain includes all or a portion of the protein identified by the NCBI sequence reference NP_001759.3, or an isoform or naturally occurring mutant or variant thereof. In some cases, the CD8 transmembrane domain includes all or a portion of the protein identified by the NCBI sequence reference XP_011531466.1, or an isoform or naturally occurring mutant or variant thereof. In some cases, the CD8 transmembrane domain includes all or a portion of the protein identified by the NCBI sequence reference NP_001171571.1, or an isoform or naturally occurring mutant or variant thereof. In some cases, the CD8 transmembrane domain includes all or a portion of the protein identified by the NCBI sequence reference NP_757362.1, or an isoform or naturally occurring mutant or variant thereof. In some cases, the CD8 transmembrane domain includes all or a portion of the protein identified by the NCBI sequence reference NP_742100.1, or an isoform or naturally occurring mutant or variant thereof. In some cases, the CD8 transmembrane domain includes all or a portion of the protein identified by the NCBI sequence reference NP_742099.1, or an isoform or naturally occurring mutant or variant thereof. In some cases, the CD8 transmembrane domain includes all or a portion of the protein identified by the NCBI sequence reference NP_004922.1, or an isoform or naturally occurring mutant or variant thereof.

Non-limiting examples of human CD8 amino acid sequences available under NCBI sequence references are as follows:

NP_001139345.1 (SEQ ID NO: 46)

MALPVTALLLPLALLLHAARPSQFRVSPLDRTWNLG

ETVELKCQVLLSNPTSGCSWLFQPRGAAASPTFLLY

LSQNKPKAAEGLDTQRFSGKRLGDTFVLTLSDFRRE

NEGYYFCSALSNSIMYFSHFVPVFLPAKPTTTPAPR

PPTPAPTIASQPLSLRPEACRPAAGGAVHTRGLDFA

CDIYIWAPLAGTCGVLLLSLVITLYCNHRNRRRVCK

CPRPVVKSGDKPSLSARYV

NP_741969.1 (SEQ ID NO: 47)

MALPVTALLLPLALLLHAARPSQFRVSPLDRTWNLG

ETVELKCQVLLSNPTSGCSWLFQPRGAAASPTFLLY

LSQNKPKAAEGLDTQRFSGKRLGDTFVLTLSDFRRE

NEGYYFCSALSNSIMYFSHFVPVFLPAKPTTTPAPR

PPTPAPTIASQPLSLRPEACRPAAGGAGNRRRVCKC

PRPVVKSGDKPSLSARYV

NP_001759.3 (SEQ ID NO: 48)

MALPVTALLLPLALLLHAARPSQFRVSPLDRTWNLG

ETVELKCQVLLSNPTSGCSWLFQPRGAAASPTFLLY

LSQNKPKAAEGLDTQRFSGKRLGDTFVLTLSDFRRE

NEGYYFCSALSNSIMYFSHFVPVFLPAKPTTTPAPR

PPTPAPTIASQPLSLRPEACRPAAGGAVHTRGLDFA

CDIYIWAPLAGTCGVLLLSLVITLYCNHRNRRRVCK

CPRPVVKSGDKPSLSARYV

XP_011531466.1 (SEQ ID NO: 49)

MRPRLWLLLAAQLTVLHGNSVLQQTPAYIKVQTNKM

VMLSCEAKISLSNMRIYWLRQRQAPSSDSHHEFLAL

WDSAKGTIHGEEVEQEKIAVFRDASRFILNLTSVKP

EDSGIYFCMIVGSPELTFGKGTQLSVVDFLPTTAQP

TKKSTLKKRVCRLPRPETQKGPLCSPITLGLLVAGV

LVLLVSLGVAIHLCCRRRRARLRFMKQKFNIVCLKI

SGFTTCCCFQILQMSREYGFGVLLQKDIGQ

NP_001171571.1 (SEQ ID NO: 50)

MRPRLWLLLAAQLTVLHGNSVLQQTPAYIKVQTNKM

VMLSCEAKISLSNMRIYWLRQRQAPSSDSHHEFLAL

WDSAKGTIHGEEVEQEKIAVFRDASRFILNLTSVKP

-continued

EDSGIYFCMIVGSPELTFGKGTQLSVVDFLPTTAQP

TKKSTLKKRVCRLPRPETQKGLKGKVYQEPLSPNAC

MDTTAILQPHRSCLTHGS

NP 757362.1 (SEQ ID NO: 51)

MRPRLWLLLAAQLTVLHGNSVLQQTPAYIKVQTNKM

VMLSCEAKISLSNMRIYWLRQRQAPSSDSHHEFLAL

WDSAKGTIHGEEVEQEKIAVFRDASRFILNLTSVKP

EDSGIYFCMIVGSPELTFGKGTQLSVVDFLPTTAQP

TKKSTLKKRVCRLPRPETQKGPLCSPITLGLLVAGV

LVLLVSLGVAIHLCCRRRRARLRFMKQPQGEGISGT

FVPQCLHGYYSNTTTSQKLLNPWILKT

NP_742100.1 (SEQ ID NO: 52)

MRPRLWLLLAAQLTVLHGNSVLQQTPAYIKVQTNKM

VMLSCEAKISLSNMRIYWLRQRQAPSSDSHHEFLAL

WDSAKGTIHGEEVEQEKIAVFRDASRFILNLTSVKP

EDSGIYFCMIVGSPELTFGKGTQLSVVDFLPTTAQP

TKKSTLKKRVCRLPRPETQKGRRRRARLRFMKQPQG

EGISGTFVPQCLHGYYSNTTTSQKLLNPWILKT

NP_742099.1 (SEQ ID NO: 53)

MRPRLWLLLAAQLTVLHGNSVLQQTPAYIKVQTNKM

VMLSCEAKISLSNMRIYWLRQRQAPSSDSHHEFLAL

WDSAKGTIHGEEVEQEKIAVFRDASRFILNLTSVKP

EDSGIYFCMIVGSPELTFGKGTQLSVVDFLPTTAQP

TKKSTLKKRVCRLPRPETQKGPLCSPITLGLLVAGV

LVLLVSLGVAIHLCCRRRRARLRFMKQLRLHPLEKC

SRMDY

NP_004922.1 (SEQ ID NO: 54)

MRPRLWLLLAAQLTVLHGNSVLQQTPAYIKVQTNKM

VMLSCEAKISLSNMRIYWLRQRQAPSSDSHHEFLAL

WDSAKGTIHGEEVEQEKIAVFRDASRFILNLTSVKP

EDSGIYFCMIVGSPELTFGKGTQLSVVDFLPTTAQP

TKKSTLKKRVCRLPRPETQKGPLCSPITLGLLVAGV

LVLLVSLGVAIHLCCRRRRARLRFMKQFYK

[0114] In some cases, the CD8 transmembrane domain is encoded by all or a portion of the nucleic acid sequence identified by the NCBI sequence reference NR_027353.1, or an isoform or naturally occurring mutant or variant thereof. In some cases, the CD8 transmembrane domain is encoded by all or a portion of the nucleic acid sequence identified by the NCBI sequence reference NM_001145873.1, or an isoform or naturally occurring mutant or variant thereof. In some cases, the CD8 transmembrane domain is encoded by all or a portion of the nucleic acid sequence identified by the

NCBI sequence reference NM_001768.6, or an isoform or naturally occurring mutant or variant thereof. In some cases, the CD8 transmembrane domain is encoded by all or a portion of the nucleic acid sequence identified by the NCBI sequence reference NM_171827.3, or an isoform or naturally occurring mutant or variant thereof. In some cases, the CD8 transmembrane domain is encoded by all or a portion of the nucleic acid sequence identified by the NCBI sequence reference XM_011533164.2, or an isoform or naturally occurring mutant or variant thereof. In some cases, the CD8 transmembrane domain is encoded by all or a portion of the nucleic acid sequence identified by the NCBI sequence reference NM_001178100.1, or an isoform or naturally occurring mutant or variant thereof. In some cases, the CD8 transmembrane domain is encoded by all or a portion of the nucleic acid sequence identified by the NCBI sequence reference NM_004931.4, or an isoform or naturally occurring mutant or variant thereof. In some cases, the CD8 transmembrane domain is encoded by all or a portion of the nucleic acid sequence identified by the NCBI sequence reference NM_172102.3, or an isoform or naturally occurring mutant or variant thereof. In some cases, the CD8 transmembrane domain is encoded by all or a portion of the nucleic acid sequence identified by the NCBI sequence reference NM_172101.3, or an isoform or naturally occurring mutant or variant thereof. In some cases, the CD8 transmembrane domain is encoded by all or a portion of the nucleic acid sequence identified by the NCBI sequence reference NM_172213.3, or an isoform or naturally occurring mutant or variant thereof. In some cases, a variant or mutant of the CD8 transmembrane domain nucleic acid sequence includes no more than 5, 4, 3, 2, or 1 deletions compared to the naturally occurring CD8 transmembrane domain nucleic acid sequence. In some cases, a variant or mutant of the CD8 transmembrane domain nucleic acid sequence includes no more than 5, 4, 3, 2, or 1 insertions compared to the naturally occurring CD8 transmembrane domain nucleic acid sequence. In some cases, a variant or mutant of the CD8 transmembrane domain nucleic acid sequence does not include deletions compared to the naturally occurring CD8 transmembrane domain nucleic acid sequence. In some cases, a variant or mutant of the CD8 transmembrane domain nucleic acid sequence does not include insertions compared to the naturally occurring CD8 transmembrane domain nucleic acid sequence. In some cases, a variant or mutant of the CD8 transmembrane domain nucleic acid sequence includes substitutions that are conservative substitutions compared to the naturally occurring CD8 transmembrane domain nucleic acid sequence.

[0115] The term "CD3-zeta transmembrane domain" as provided herein includes any of the recombinant or naturally-occurring forms of the transmembrane domain of CD3-zeta, or variants or homologs thereof that maintain CD3-zeta transmembrane domain activity (e.g. within at least 50%, 80%, 90%, 95%, 96%, 97%, 98%, 99% or 100% activity compared to the CD3-zeta transmembrane domain). In some aspects, the variants or homologs have at least 90%, 95%, 96%, 97%, 98%, 99% or 100% amino acid sequence identity across the whole sequence or a portion of the sequence (e.g. a 50, 100, 150 or 200 continuous amino acid portion) compared to a naturally occurring CD3-zeta transmembrane domain polypeptide. In some cases, the CD3-zeta transmembrane domain is a human CD3- zeta transmembrane domain protein. In some cases, a variant or mutant of the CD3-zeta transmembrane domain protein includes no more than 5, 4, 3, 2, or 1 deletions compared to the naturally occurring CD3-zeta transmembrane domain protein. In some cases, a variant or mutant of the CD3-zeta transmembrane domain protein includes no more than 5, 4, 3, 2, or 1 insertions compared to the naturally occurring CD3-zeta transmembrane domain protein. In some cases, a variant or mutant of the CD3-zeta transmembrane domain protein does not include deletions compared to the naturally occurring CD3-zeta transmembrane domain protein. In some cases, a variant or mutant of the CD3-zeta transmembrane domain protein does not include insertions compared to the naturally occurring CD3-zeta transmembrane domain protein. In some cases, a variant or mutant of the CD3-zeta transmembrane domain protein includes substitutions that are conservative substitutions compared to the naturally occurring CD3-zeta transmembrane domain protein. In some cases, the CD3-zeta transmembrane domain includes all or a portion of the protein identified by the NCBI sequence reference NP_000725.1, or an isoform or naturally occurring mutant or variant thereof. In some cases, the CD3-zeta transmembrane domain includes all or a portion of the protein identified by the NCBI sequence reference NP_932170.1, or an isoform or naturally occurring mutant or variant thereof. Non-limiting examples of human CD3-zeta amino acid sequences available under NCBI sequence references are as follows:

NP_000725.1 (SEQ ID NO: 55)

MKWKALFTAAILQAQLPITEAQSFGLLDPKLCYLLD

GILFIYGVILTALFLRVKFSRSADAPAYQQGQNQLY

NELNLGRREEYDVLDKRRGRDPEMGGKPRRKNPQEG

LYNELQKDKMAEAYSEIGMKGERRRGKGHDGLYQGL

STATKDTYDALHMQALPPR

NP_932170.1 (SEQ ID NO: 56)

MKWKALFTAAILQAQLPITEAQSFGLLDPKLCYLLD

GILFIYGVILTALFLRVKFSRSADAPAYQQGQNQLY

NELNLGRREEYDVLDKRRGRDPEMGGKPQRRKNPQE

GLYNELQKDKMAEAYSEIGMKGERRRGKGHDGLYQG

LSTATKDTYDALHMQALPPR

[0116] In some cases, the CD3-zeta transmembrane domain is encoded by all or a portion of the nucleic acid sequence identified by the NCBI sequence reference NM_000734.3, or an isoform or naturally occurring mutant or variant thereof. In some cases, the CD3-zeta transmembrane domain is encoded by all or a portion of the nucleic acid sequence identified by the NCBI sequence reference NM_198053.2, or an isoform or naturally occurring mutant or variant thereof. In some cases, a variant or mutant of the CD3-zeta transmembrane domain nucleic acid sequence includes no more than 5, 4, 3, 2, or 1 deletions compared to the naturally occurring CD3-zeta transmembrane domain nucleic acid sequence. In some cases, a variant or mutant of the CD3-zeta transmembrane domain nucleic acid sequence includes no more than 5, 4, 3, 2, or 1 insertions compared to the naturally occurring CD3-zeta transmembrane domain

nucleic acid sequence. In some cases, a variant or mutant of the CD3-zeta transmembrane domain nucleic acid sequence does not include deletions compared to the naturally occurring CD3-zeta transmembrane domain nucleic acid sequence. In some cases, a variant or mutant of the CD3-zeta transmembrane domain nucleic acid sequence does not include insertions compared to the naturally occurring CD3-zeta transmembrane domain nucleic acid sequence. In some cases, a variant or mutant of the CD3-zeta transmembrane domain nucleic acid sequence includes substitutions that are conservative substitutions compared to the naturally occurring CD3-zeta transmembrane domain nucleic acid sequence.

[0117] The term "CD28 co-stimulatory domain" as provided herein includes any of the recombinant or naturally-occurring forms of the co-stimulatory domain of CD28, or variants or homologs thereof that maintain CD28 co-stimulatory domain activity (e.g. within at least 50%, 80%, 90%, 95%, 96%, 97%, 98%, 99% or 100% activity compared to the CD28 co-stimulatory domain). In some aspects, the variants or homologs have at least 90%, 95%, 96%, 97%, 98%, 99% or 100% amino acid sequence identity across the whole sequence or a portion of the sequence (e.g. a 50, 100, 150 or 200 continuous amino acid portion) compared to a naturally occurring CD28 co-stimulatory domain polypeptide. In some cases, the CD28 co-stimulatory domain amino acid sequence includes the sequence of RSKRSRGGHSDYMNMTPRRPGPTRKHYQPYAPPRDFAAYRS (SEQ ID NO:7). In some cases, the CD28 co-stimulatory domain amino acid sequence is the sequence of RSKRSRLLHSDYMNMTPRRPGPTRKHYQPYAPPRDFAAYRS (SEQ ID NO:8).

[0118] In some cases, the CD28 co-stimulatory domain is a human CD28 co-stimulatory domain protein. In some cases, a variant or mutant of the CD28 co-stimulatory domain protein includes no more than 5, 4, 3, 2, or 1 deletions compared to the naturally occurring CD28 co-stimulatory domain protein. In some cases, a variant or mutant of the CD28 co-stimulatory domain protein includes no more than 5, 4, 3, 2, or 1 insertions compared to the naturally occurring CD28 co-stimulatory domain protein. In some cases, a variant or mutant of the CD28 co-stimulatory domain protein does not include deletions compared to the naturally occurring CD28 co-stimulatory domain protein. In some cases, a variant or mutant of the CD28 co-stimulatory domain protein does not include insertions compared to the naturally occurring CD28 co-stimulatory domain protein. In some cases, a variant or mutant of the CD28 co-stimulatory domain protein includes substitutions that are conservative substitutions compared to the naturally occurring CD28 co-stimulatory domain protein. In some cases, the CD28 co-stimulatory domain includes all or a portion of the protein identified by the NCBI sequence reference NP_001230006.1, or an isoform or naturally occurring mutant or variant thereof. In some cases, the CD28 co-stimulatory domain includes all or a portion of the protein identified by the NCBI sequence reference NP_001230007.1, or an isoform or naturally occurring mutant or variant thereof. In some cases, the CD28 co-stimulatory domain includes all or a portion of the protein identified by the NCBI sequence reference NP_006130.1, or an isoform or naturally occurring mutant or variant thereof. Non-limiting examples of human CD28 amino acid sequences available under NCBI sequence references are as follows:

NP_001230006.1

(SEQ ID NO: 57)

MLRLLLALNLFPSIQVTGNKILVKQSPMLVAYDNAV

NLSWKHLCPSPLFPGPSKPFWVLVVVGGVLACYSLL

VTVAFIIFWVRSKRSRLLHSDYMNMTPRRPGPTRKH

YQPYAPPRDFAAYRS

NP_001230007.1

(SEQ ID NO: 58)

MLRLLLALNLFPSIQVTGKHLCPSPLFPGPSKPFWV

LVVVGGVLACYSLLVTVAFIIFWVRSKRSRLLHSDY

MNMTPRRPGPTRKHYQPYAPPRDFAAYRS

NP_006130.1

(SEQ ID NO: 59)

MLRLLLALNLFPSIQVTGNKILVKQSPMLVAYDNAV

NLSCKYSYNLFSREFRASLHKGLDSAVEVCVVYGNY

SQQLQVYSKTGFNCDGKLGNESVTFYLQNLYVNQTD

IYFCKIEVMYPPPYLDNEKSNGTIIHVKGKHLCPSP

LFPGPSKPFWVLVVVGGVLACYSLLVTVAFIIFWVR

SKRSRLLHSDYMNMTPRRPGPTRKHYQPYAPPRDFA

AYRS

[0119] In some cases, the CD28 co-stimulatory domain is encoded by all or a portion of the nucleic acid sequence identified by the NCBI sequence reference NM_001243077.1, or an isoform or naturally occurring mutant or variant thereof. In some cases, the CD28 co-stimulatory domain is encoded by all or a portion of the nucleic acid sequence identified by the NCBI sequence reference NM_001243078.1, or an isoform or naturally occurring mutant or variant thereof. In some cases, the CD28 co-stimulatory domain is encoded by all or a portion of the nucleic acid sequence identified by the NCBI sequence reference NM_006139.3, or an isoform or naturally occurring mutant or variant thereof. In some cases, a variant or mutant of the CD28 co-stimulatory domain nucleic acid sequence includes no more than 5, 4, 3, 2, or 1 deletions compared to the naturally occurring CD28 co-stimulatory domain nucleic acid sequence. In some cases, a variant or mutant of the CD28 co-stimulatory domain nucleic acid sequence includes no more than 5, 4, 3, 2, or 1 insertions compared to the naturally occurring CD28 transmembrane domain nucleic acid sequence. In some cases, a variant or mutant of the CD28 co-stimulatory domain nucleic acid sequence does not include deletions compared to the naturally occurring CD28 co-stimulatory domain nucleic acid sequence. In some cases, a variant or mutant of the CD28 co-stimulatory domain nucleic acid sequence does not include insertions compared to the naturally occurring CD28 co-stimulatory domain nucleic acid sequence. In some cases, a variant or mutant of the CD28 co-stimulatory domain nucleic acid sequence includes substitutions that are conservative substitutions compared to the naturally occurring CD28 co-stimulatory domain nucleic acid sequence.

[0120] The term "4-1BB co-stimulatory domain" as provided herein includes any of the recombinant or naturally-occurring forms of the co-stimulatory domain of 4-1BB, or variants or homologs thereof that maintain 4-1BB co-stimu-

latory domain activity (e.g. within at least 50%, 80%, 90%, 95%, 96%, 97%, 98%, 99% or 100% activity compared to the 4-1BB co-stimulatory domain). In some aspects, the variants or homologs have at least 90%, 95%, 96%, 97%, 98%, 99% or 100% amino acid sequence identity across the whole sequence or a portion of the sequence (e.g. a 50, 100, 150 or 200 continuous amino acid portion) compared to a naturally occurring 4-1BB co-stimulatory domain polypeptide. In some cases, the 4-1BB co-stimulatory domain is a human 4-1BB co-stimulatory domain protein. In some cases, a variant or mutant of the 4-1BB co-stimulatory domain protein includes no more than 5, 4, 3, 2, or 1 deletions compared to the naturally occurring 4-1BB co-stimulatory domain protein. In some cases, a variant or mutant of the 4-1BB co-stimulatory domain protein includes no more than 5, 4, 3, 2, or 1 insertions compared to the naturally occurring 4-1BB co-stimulatory domain protein. In some cases, a variant or mutant of the 4-1BB co-stimulatory domain protein does not include deletions compared to the naturally occurring 4-1BB co-stimulatory domain protein. In some cases, a variant or mutant of the 4-1BB co-stimulatory domain protein does not include insertions compared to the naturally occurring 4-1BB co-stimulatory domain protein. In some cases, a variant or mutant of the 4-1BB co-stimulatory domain protein includes substitutions that are conservative substitutions compared to the naturally occurring 4-1BB co-stimulatory domain protein. In some cases, the 4-1BB co-stimulatory domain protein includes the amino acid sequence KRGRKKLLYIFKQPFMRPVQTTQEEDGCSCRFPEEEEGGCEL (SEQ ID NO:14). In some cases, the 4-1BB co-stimulatory domain protein amino acid sequence has at least or about 50%, 60%, 70%, 75%, 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% sequence identify to SEQ ID NO:14. In some cases, the 4-1BB co-stimulatory domain includes all or a portion of the protein identified by the NCBI sequence reference NP_001552.2 or an isoform or naturally occurring mutant or variant thereof. Non-limiting examples of human 4-1BB amino acid sequences available under NCBI sequence references are as follows:

NP_001552.2 (SEQ ID NO: 15)

MGNSCYNIVATLLLVLNFERTRSLQDPCSNCPAGTF

CDNNRNQICSPCPPNSFSSAGGQRTCDICRQCKGVF

RTRKECSSTSNAECDCTPGFHCLGAGCSMCEQDCKQ

GQELTKKGCKDCCFGTFNDQKRGICRPWTNCSLDGK

SVLVNGTKERDVVCGPSPADLSPGASSVTPPAPARE

PGHSPQIISFFLALTSTALLFLLFFLTLRFSVVKRG

RKKLLYIFKQPFMRPVQTTQEEDGCSCRFPEEEEGG

CEL

[0121] In some cases, the 4-1BB co-stimulatory domain is encoded by all or a portion of the nucleic acid sequence identified by the NCBI sequence reference NM_001561.5 or an isoform or naturally occurring mutant or variant thereof. In some cases, a variant or mutant of the 4-1BB co-stimulatory domain nucleic acid sequence includes no more than 5, 4, 3, 2, or 1 deletions compared to the naturally occurring 4-1BB co-stimulatory domain nucleic acid sequence. In some cases, a variant or mutant of the 4-1BB co-stimulatory domain nucleic acid sequence includes no more than 5, 4, 3, 2, or 1 insertions compared to the naturally occurring 4-1BB co-stimulatory domain nucleic acid sequence. In some cases, a variant or mutant of the 4-1BB co-stimulatory domain nucleic acid sequence does not include deletions compared to the naturally occurring 4-1BB co-stimulatory domain nucleic acid sequence. In some cases, a variant or mutant of the 4-1BB co-stimulatory domain nucleic acid sequence does not include insertions compared to the naturally occurring 4-1BB co-stimulatory domain nucleic acid sequence. In some cases, a variant or mutant of the 4-1BB co-stimulatory domain nucleic acid sequence includes substitutions that are conservative substitutions compared to the naturally occurring 4-1BB co-stimulatory domain nucleic acid sequence.

[0122] The term "ICOS co-stimulatory domain" as provided herein includes any of the recombinant or naturally-occurring forms of the co-stimulatory domain of ICOS, or variants or homologs thereof that maintain ICOS co-stimulatory domain activity (e.g. within at least 50%, 80%, 90%, 95%, 96%, 97%, 98%, 99% or 100% activity compared to the ICOS co-stimulatory domain). In some aspects, the variants or homologs have at least 90%, 95%, 96%, 97%, 98%, 99% or 100% amino acid sequence identity across the whole sequence or a portion of the sequence (e.g. a 50, 100, 150 or 200 continuous amino acid portion) compared to a naturally occurring ICOS co-stimulatory domain polypeptide. In some cases, the ICOS co-stimulatory domain amino acid sequence includes the sequence of CWLTKKKYSSSVHDPNGEYMFMRAVNTAKKSRLTDVTL (SEQ ID NO:31). In some cases, the ICOS co-stimulatory domain is a human ICOS co-stimulatory domain protein. In some cases, a variant or mutant of the ICOS co-stimulatory domain protein includes no more than 5, 4, 3, 2, or 1 deletions compared to the naturally occurring ICOS co-stimulatory domain protein. In some cases, a variant or mutant of the ICOS co-stimulatory domain protein includes no more than 5, 4, 3, 2, or 1 insertions compared to the naturally occurring ICOS co-stimulatory domain protein. In some cases, a variant or mutant of the ICOS co-stimulatory domain protein does not include deletions compared to the naturally occurring ICOS co-stimulatory domain protein. In some cases, a variant or mutant of the ICOS co-stimulatory domain protein does not include insertions compared to the naturally occurring ICOS co-stimulatory domain protein. In some cases, a variant or mutant of the ICOS co-stimulatory domain protein includes substitutions that are conservative substitutions compared to the naturally occurring ICOS co-stimulatory domain protein. In some cases, the ICOS co-stimulatory domain includes all or a portion of the protein identified by the NCBI sequence reference NP_036224.1, or an isoform or naturally occurring mutant or variant thereof. Non-limiting examples of human ICOS amino acid sequences available under NCBI sequence references are as follows:

NP_036224.1

(SEQ ID NO: 16)

MKSGLWYFFLFCLRIKVLTGEINGSANYEMFIFHNGGVQILCKYPDIVQQ

FKMQLLKGGQILCDLTKTKGSGNTVSIKSLKFCHSQLSNNSVSFFLYNLD

HSHANYYFCNLSIFDPPPPFKVTLTGGYLHIYESQLCCQLKFWLPIGCAAF

VVVCILGCILICWLTKKKYSSSVHDPNGEYMFMRAVNTAKKSRLTDVTL

[0123] In some cases, the ICOS co-stimulatory domain is encoded by all or a portion of the nucleic acid sequence identified by the NCBI sequence reference NM_012092.3, or an isoform or naturally occurring mutant or variant thereof. In some cases, a variant or mutant of the ICOS co-stimulatory domain nucleic acid sequence includes no more than 5, 4, 3, 2, or 1 deletions compared to the naturally occurring ICOS co-stimulatory domain nucleic acid sequence. In some cases, a variant or mutant of the ICOS co-stimulatory domain nucleic acid sequence includes no more than 5, 4, 3, 2, or 1 insertions compared to the naturally occurring ICOS co-stimulatory domain nucleic acid sequence. In some cases, a variant or mutant of the ICOS co-stimulatory domain nucleic acid sequence does not include deletions compared to the naturally occurring ICOS co-stimulatory domain nucleic acid sequence. In some cases, a variant or mutant of the ICOS co-stimulatory domain nucleic acid sequence does not include insertions compared to the naturally occurring ICOS co-stimulatory domain nucleic acid sequence. In some cases, a variant or mutant of the ICOS co-stimulatory domain nucleic acid sequence includes substitutions that are conservative substitutions compared to the naturally occurring ICOS co-stimulatory domain nucleic acid sequence.

[0124] The term "OX-40 co-stimulatory domain" as provided herein includes any of the recombinant or naturally-occurring forms of the co-stimulatory domain of OX-40, or variants or homologs thereof that maintain OX-40 co-stimulatory domain activity (e.g. within at least 50%, 80%, 90%, 95%, 96%, 97%, 98%, 99% or 100% activity compared to the OX-40 co-stimulatory domain). In some aspects, the variants or homologs have at least 90%, 95%, 96%, 97%, 98%, 99% or 100% amino acid sequence identity across the whole sequence or a portion of the sequence (e.g. a 50, 100, 150 or 200 continuous amino acid portion) compared to a naturally occurring OX-40 co-stimulatory domain polypeptide. In some cases, the OX-40 co-stimulatory domain amino acid sequence includes the sequence of ALYLLRRDQRLPPDAHKPPGGGSFRTPIQEEQADAH-STLAKI (SEQ ID NO:32). In some cases, the OX-40 co-stimulatory domain is a human OX-40 co-stimulatory domain protein. In some cases, a variant or mutant of the OX-40 co-stimulatory domain protein includes no more than 5, 4, 3, 2, or 1 deletions compared to the naturally occurring OX-40 co-stimulatory domain protein. In some cases, a variant or mutant of the OX-40 co-stimulatory domain protein includes no more than 5, 4, 3, 2, or 1 insertions compared to the naturally occurring OX-40 co-stimulatory domain protein. In some cases, a variant or mutant of the OX-40 co-stimulatory domain protein does not include deletions compared to the naturally occurring OX-40 co-stimulatory domain protein. In some cases, a variant or mutant of the OX-40 co-stimulatory domain protein does not include insertions compared to the naturally occurring OX-40 co-stimulatory domain protein. In some cases, a variant or mutant of the OX-40 co-stimulatory domain protein includes substitutions that are conservative substitutions compared to the naturally occurring OX-40 co-stimulatory domain protein. In some cases, the OX-40 co-stimulatory domain includes all or a portion of the protein identified by the NCBI sequence reference NP_003318.1, or an isoform or naturally occurring mutant or variant thereof. Non-limiting examples of human OX-40 amino acid sequences available under NCBI sequence references are as follows:

NP_003318.1

(SEQ ID NO: 60)

MCVGARRLGRGPCAALLLLGLGLSTVTGLHCVGDTYPSNDRCCHECRPGN

GMVSRCSRSQNTVCRPCGPGFYNDVVSSKPCKPCTWCNLRSGSERKQLCT

ATQDTVCRCRAGTQPLDSYKPGVDCAPCPPGHFSPGDNQACKPWTNCTLA

GKHTLQPASNSSDAICEDRDPPATQPQETQGPPARPITVQPTEAWPRTSQ

GPSTRPVEVPGGRAVAAILGLGLVLGLLGPLAILLALYLLRRDQRLPPDA

HKPPGGGSFRTPIQEEQADAHSTLAKI

[0125] In some cases, the OX-40 co-stimulatory domain is encoded by all or a portion of the nucleic acid sequence identified by the NCBI sequence reference NM_003327.3, or an isoform or naturally occurring mutant or variant thereof. In some cases, a variant or mutant of the OX-40 co-stimulatory domain nucleic acid sequence includes no more than 5, 4, 3, 2, or 1 deletions compared to the naturally occurring OX-40 co-stimulatory domain nucleic acid sequence. In some cases, a variant or mutant of the OX-40 co-stimulatory domain nucleic acid sequence includes no more than 5, 4, 3, 2, or 1 insertions compared to the naturally occurring OX-40 co-stimulatory domain nucleic acid sequence. In some cases, a variant or mutant of the OX-40 co-stimulatory domain nucleic acid sequence does not include deletions compared to the naturally occurring OX-40 co-stimulatory domain nucleic acid sequence. In some cases, a variant or mutant of the OX-40 co-stimulatory domain nucleic acid sequence does not include insertions compared to the naturally occurring OX-40 co-stimulatory domain nucleic acid sequence. In some cases, a variant or mutant of the OX-40 co-stimulatory domain nucleic acid sequence includes substitutions that are conservative substitutions compared to the naturally occurring OX-40 co-stimulatory domain nucleic acid sequence.

[0126] The term "CTLA-4 cytoplasmic domain" as provided herein includes any of the recombinant or naturally-occurring forms of the co-stimulatory domain of CTLA-4, or variants or homologs thereof that maintain CTLA-4 cytoplasmic domain activity (e.g. within at least 50%, 80%, 90%, 95%, 96%, 97%, 98%, 99% or 100% activity compared to the CTLA-4 cytoplasmic domain). In some aspects, the variants or homologs have at least 90%, 95%, 96%, 97%, 98%, 99% or 100% amino acid sequence identity across the whole sequence or a portion of the sequence (e.g. a 50, 100, 150 or 200 continuous amino acid portion) compared to a naturally occurring CTLA-4 cytoplasmic domain polypeptide. In some cases, CTLA-4 cytoplasmic domain protein is a human CTLA-4 cytoplasmic domain protein. In some cases, the CTLA-4 cytoplasmic domain includes no more than 5, 4, 3, 2, or 1 deletions. In some cases, the CTLA-4 cytoplasmic domain protein includes no more than 5, 4, 3,

2, or 1 insertions. In some cases, the CTLA-4 cytoplasmic domain protein does not include deletions. In some cases, CTLA-4 cytoplasmic domain protein does not include insertions. In some cases, the CTLA-4 cytoplasmic domain protein includes substitutions that are conservative substitutions. In some cases, CTLA-4 cytoplasmic domain protein includes the sequence AVSLSKMLKKRSPLTTGVYVKMPPTEPECEKQFQPYFIPIN (SEQ ID NO:17). In some cases, CTLA-4 cytoplasmic domain protein is the sequence SEQ ID NO:17. In some cases, the CTLA-4 cytoplasmic domain amino acid sequence has at least or about 50%, 60%, 70%, 75%, 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% sequence identify to SEQ ID NO: 17. In some cases, the CTLA-4 cytoplasmic domain is a human CTLA-4 cytoplasmic domain protein. In some cases, a variant or mutant of the CTLA-4 cytoplasmic domain protein includes no more than 5, 4, 3, 2, or 1 deletions compared to the naturally occurring CTLA-4 cytoplasmic domain protein. In some cases, a variant or mutant of the CTLA-4 cytoplasmic domain protein includes no more than 5, 4, 3, 2, or 1 insertions compared to the naturally occurring CTLA-4 cytoplasmic domain protein. In some cases, a variant or mutant of the CTLA-4 cytoplasmic domain protein does not include deletions compared to the naturally occurring CTLA-4 cytoplasmic domain protein. In some cases, a variant or mutant of the CTLA-4 cytoplasmic domain protein does not include insertions compared to the naturally occurring CTLA-4 cytoplasmic domain protein. In some cases, a variant or mutant of the CTLA-4 cytoplasmic domain protein includes substitutions that are conservative substitutions compared to the naturally occurring CTLA-4 cytoplasmic domain protein. In some cases, the CTLA-4 cytoplasmic domain includes all or a portion of the protein identified by the NCBI sequence reference NP_001032720.1, or an isoform or naturally occurring mutant or variant thereof. In some cases, the CTLA-4 cytoplasmic domain includes all or a portion of the protein identified by the NCBI sequence reference NP_005205.2, or an isoform or naturally occurring mutant or variant thereof. Non-limiting examples of human CTLA-4 amino acid sequences available under NCBI sequence references are as follows:

NP_001032720.1

(SEQ ID NO: 61)

MACLGFQRHKAQLNLATRTWPCTLLFFLLFIPVFCKAMHVAQPAVVLASS

RGIASFVCEYASPGKATEVRVTVLRQADSQVTEVCAATYMMGNELTFLDD

SICTGTSSGNQVNLTIQGLRAMDTGLYICKVELMYPPPYYLGIGNGTQIY

VIAKEKKPSYNRGLCENAPNRARM

NP_005205.2

(SEQ ID NO: 62)

MACLGFQRHKAQLNLATRTWPCTLLFFLLFIPVFCKAMHVAQPAVVLASS

RGIASFVCEYASPGKATEVRVTVLRQADSQVTEVCAATYMMGNELTFLDD

SICTGTSSGNQVNLTIQGLRAMDTGLYICKVELMYPPPYYLGIGNGTQIY

VIDPEPCPDSDFLLWILAAVSSGLFFYSFLLTAVSLSKMLKKRSPLTTGV

YVKMPPTEPECEKQFQPYFIPIN

[0127] In some cases, the CTLA-4 cytoplasmic domain is encoded by all or a portion of the nucleic acid sequence identified by the NCBI sequence reference NM_001037631.3, or an isoform or naturally occurring mutant or variant thereof. In some cases, the CTLA-4 cytoplasmic domain is encoded by all or a portion of the nucleic acid sequence identified by the NCBI sequence reference NM_005214.5, or an isoform or naturally occurring mutant or variant thereof. In some cases, a variant or mutant of the CTLA-4 cytoplasmic domain nucleic acid sequence includes no more than 5, 4, 3, 2, or 1 deletions compared to the naturally occurring CTLA-4 cytoplasmic domain nucleic acid sequence. In some cases, a variant or mutant of the CTLA-4 cytoplasmic domain nucleic acid sequence includes no more than 5, 4, 3, 2, or 1 insertions compared to the naturally occurring CTLA-4 cytoplasmic domain nucleic acid sequence. In some cases, a variant or mutant of the CTLA-4 cytoplasmic domain nucleic acid sequence does not include deletions compared to the naturally occurring CTLA-4 cytoplasmic domain nucleic acid sequence. In some cases, a variant or mutant of the CTLA-4 cytoplasmic domain nucleic acid sequence does not include insertions compared to the naturally occurring CTLA-4 cytoplasmic domain nucleic acid sequence. In some cases, a variant or mutant of the CTLA-4 cytoplasmic domain nucleic acid sequence includes substitutions that are conservative substitutions compared to the naturally occurring CTLA-4 cytoplasmic domain nucleic acid sequence.

[0128] The term "PD-1 co-stimulatory domain" as provided herein includes any of the recombinant or naturally-occurring forms of the co-stimulatory domain of PD-1, or variants or homologs thereof that maintain PD-1 co-stimulatory domain activity (e.g. within at least 50%, 80%, 90%, 95%, 96%, 97%, 98%, 99% or 100% activity compared to the PD-1 co-stimulatory domain). In some aspects, the variants or homologs have at least 90%, 95%, 96%, 97%, 98%, 99% or 100% amino acid sequence identity across the whole sequence or a portion of the sequence (e.g. a 50, 100, 150 or 200 continuous amino acid portion) compared to a naturally occurring PD-1 co-stimulatory domain polypeptide. In some cases, the PD-I co-stimulatory domain amino acid sequence includes the sequence of CSRAARGTIGARRTGQPLKEDPSAVPVFSVDYGELDFQWREKTPEPPVPCVPEQTEY ATIVFPSGMGTSSPARRGSADGPRSAQPLRPEDGHCSWPL (SEQ ID NO:33). In some cases, the PD-1 co-stimulatory domain" is a human PD-1 co-stimulatory domain protein. In some cases, a variant or mutant of the PD-1 co-stimulatory domain protein includes no more than 5, 4, 3, 2, or 1 deletions compared to the naturally occurring PD-1 co-stimulatory domain protein. In some cases, a variant or mutant of the PD-1 co-stimulatory domain protein includes no more than 5, 4, 3, 2, or 1 insertions compared to the naturally occurring PD-1 co-stimulatory domain protein. In some cases, a variant or mutant of the PD-1 co-stimulatory domain protein does not include deletions compared to the naturally occurring PD-1 co-stimulatory domain protein. In some cases, a variant or mutant of the PD-1 co-stimulatory domain protein does not include insertions compared to the naturally occurring PD-1 co-stimulatory domain protein. In some cases, a variant or mutant of the PD-1 co-stimulatory domain protein includes substitutions that are conservative substitutions compared to the naturally occurring PD-1 co-stimulatory domain protein. In some cases, the PD-1 co-stimulatory domain includes all or a portion of the protein identified by the NCBI sequence reference NP_005009.2, or an isoform or naturally occurring

mutant or variant thereof. Non-limiting examples of human PD-1 amino acid sequences available under NCBI sequence references are as follows:

NP_005009.2

(SEQ ID NO: 63)

MQIPQAPWPVVWAVLQLGWRPGWFLDSPDRPWNPPTFSPALLVVTEGDNA

TFTCSFSNTSESFVLNWYRMSPSNQTDKLAAFPEDRSQPGQDCRFRVTQL

PNGRDFHMSVVRARRNDSGTYLCGAISLAPKAQIKESLRAELRVTERRAE

VPTAHPSPSPRPAGQFQTLVVGVVGGLLGSLVLLVWVLAVICSRAARGTI

GARRTGQPLKEDPSAVPVFSVDYGELDFQWREKTPEPPVPCVPEQTEYAT

IVFPSGMGTSSPARRGSADGPRSAQPLRPEDGHCSWPL

[0129] In some cases, the PD-1 co-stimulatory domain is encoded by all or a portion of the nucleic acid sequence identified by the NCBI sequence reference NM_005018.2, or an isoform or naturally occurring mutant or variant thereof. In some cases, a variant or mutant of the PD-1 co-stimulatory domain nucleic acid sequence includes no more than 5, 4, 3, 2, or 1 deletions compared to the naturally occurring PD-1 co-stimulatory domain nucleic acid sequence. In some cases, a variant or mutant of the PD-1 co-stimulatory domain nucleic acid sequence includes no more than 5, 4, 3, 2, or 1 insertions compared to the naturally occurring PD-1 co-stimulatory domain nucleic acid sequence. In some cases, a variant or mutant of the PD-1 co-stimulatory domain nucleic acid sequence does not include deletions compared to the naturally occurring PD-1 co-stimulatory domain nucleic acid sequence. In some cases, a variant or mutant of the PD-1 co-stimulatory domain nucleic acid sequence does not include insertions compared to the naturally occurring PD-1 co-stimulatory domain nucleic acid sequence. In some cases, a variant or mutant of the PD-1 co-stimulatory domain nucleic acid sequence includes substitutions that are conservative substitutions compared to the naturally occurring PD-1 co-stimulatory domain nucleic acid sequence.

[0130] The term "GITR co-stimulatory domain" as provided herein includes any of the recombinant or naturally-occurring forms of the co-stimulatory domain of GITR, or variants or homologs thereof that maintain GITR co-stimulatory domain activity (e.g. within at least 50%, 80%, 90%, 95%, 96%, 97%, 98%, 99% or 100% activity compared to the GITR co-stimulatory domain). In some aspects, the variants or homologs have at least 90%, 95%, 96%, 97%, 98%, 99% or 100% amino acid sequence identity across the whole sequence or a portion of the sequence (e.g. a 50, 100, 150 or 200 continuous amino acid portion) compared to a naturally occurring GITR co-stimulatory domain polypeptide. In some cases, the GITR co-stimulatory domain amino acid sequence includes the sequence of QLGLHIWQLRSQCMWPRETQLLLEVPPSTEDARSCQFPEEERGERSAEEKGRLGDL WV (SEQ ID NO:67) In some cases, the GITR co-stimulatory domain is a human GITR co-stimulatory domain protein. In some cases, a variant or mutant of the GITR co-stimulatory domain protein includes no more than 5, 4, 3, 2, or 1 deletions compared to the naturally occurring GITR co-stimulatory domain protein. In some cases, a variant or mutant of the GITR co-stimulatory domain protein includes no more than 5, 4, 3, 2, or 1 insertions compared to the naturally occurring GITR co-stimulatory domain protein. In some cases, a variant or mutant of the GITR co-stimulatory domain protein does not include deletions compared to the naturally occurring GITR co-stimulatory domain protein. In some cases, a variant or mutant of the GITR co-stimulatory domain protein does not include insertions compared to the naturally occurring GITR co-stimulatory domain protein. In some cases, a variant or mutant of the GITR co-stimulatory domain protein includes substitutions that are conservative substitutions compared to the naturally occurring GITR co-stimulatory domain protein. In some cases, the GITR co-stimulatory domain includes all or a portion of the protein identified by the NCBI sequence reference NP_004186.1, or an isoform or naturally occurring mutant or variant thereof. In some cases, the GITR co-stimulatory domain includes all or a portion of the protein identified by the NCBI sequence reference NP_683699.1, or an isoform or naturally occurring mutant or variant thereof. In some cases, the GITR co-stimulatory domain includes all or a portion of the protein identified by the NCBI sequence reference NP_683700.1, or an isoform or naturally occurring mutant or variant thereof. Non-limiting examples of human GITR amino acid sequences available under NCBI sequence references are as follows:

NP_004186.1

(SEQ ID NO: 64)

MAQHGAMGAFRALCGLALLCALSLGQRPTGGPGCGPGRLLLGTGTDARCC

RVHTTRCCRDYPGEECCSEWDCMCVQPEFHCGDPCCTTCRHHPCPPGQGV

QSQGKFSFGFQCIDCASGTFSGGHEGHCKPWTDCTQFGFLTVFPGNKTHN

AVCVPGSPPAEPLGWLTVVLLAVAACVLLLTSAQLGLHIWQLRSQCMWPR

ETQLLLEVPPSTEDARSCQFPEEERGERSAEEKGRLGDLWV

NP_683699.1

(SEQ ID NO: 65)

MAQHGAMGAFRALCGLALLCALSLGQRPTGGPGCGPGRLLLGTGTDARCC

RVHTTRCCRDYPGEECCSEWDCMCVQPEFHCGDPCCTTCRHHPCPPGQGV

QSQGKFSFGFQCIDCASGTFSGGHEGHCKPWTDCCWRCRRRPKTPEAASS

PRKSGASDRQRRRGGWETCGCEPGRPPGPPTAASPSPGAPQAAGALRSAL

GRALLPWQQKWVQEGGSDQRPGPCSSAAAAGPCRRERETQSWPPSSLAGP

DGVGS

NP_683700.1

(SEQ ID NO: 66)

MAQHGAMGAFRALCGLALLCALSLGQRPTGGPGCGPGRLLLGTGTDARCC

RVHTTRCCRDYPGEECCSEWDCMCVQPEFHCGDPCCTTCRHHPCPPGQGV

QSQGKFSFGFQCIDCASGTFSGGHEGHCKPWTDCTQFGFLTVFPGNKTHN

AVCVPGSPPAEPLGWLTVVLLAVAACVLLLTSAQLGLHIWQLRKTQLLLE

VPPSTEDARSCQFPEEERGERSAEEKGRLGDLWV

[0131] In some cases, the GITR co-stimulatory domain is encoded by all or a portion of the nucleic acid sequence identified by the NCBI sequence reference NM_148902.1, or an isoform or naturally occurring mutant or variant thereof. In some cases, the GITR co-stimulatory domain is encoded by all or a portion of the nucleic acid sequence identified by the NCBI sequence reference NM_004195.2, or an isoform or naturally occurring mutant or variant thereof. In some cases, the GITR co-stimulatory domain is

encoded by all or a portion of the nucleic acid sequence identified by the NCBI sequence reference NM_148901.1, or an isoform or naturally occurring mutant or variant thereof. In some cases, a variant or mutant of the GITR co-stimulatory domain nucleic acid sequence includes no more than 5, 4, 3, 2, or 1 deletions compared to the naturally occurring GITR co-stimulatory domain nucleic acid sequence. In some cases, a variant or mutant of the GITR co-stimulatory domain nucleic acid sequence includes no more than 5, 4, 3, 2, or 1 insertions compared to the naturally occurring GITR co-stimulatory domain nucleic acid sequence. In some cases, a variant or mutant of the GITR co-stimulatory domain nucleic acid sequence does not include deletions compared to the naturally occurring GITR co-stimulatory domain nucleic acid sequence. In some cases, a variant or mutant of the GITR co-stimulatory domain nucleic acid sequence does not include insertions compared to the naturally occurring GITR co-stimulatory domain nucleic acid sequence. In some cases, a variant or mutant of the GITR co-stimulatory domain nucleic acid sequence includes substitutions that are conservative substitutions compared to the naturally occurring GITR co-stimulatory domain nucleic acid sequence.

[0132] The term "CD3ζ intracellular T-cell signaling domain" as provided herein includes any of the recombinant or naturally-occurring forms of the CD3ζ intracellular T-cell signaling domain, or variants or homologs thereof that maintain CD3ζ intracellular T-cell signaling domain activity (e.g. within at least 50%, 80%, 90%, 95%, 96%, 97%, 98%, 99% or 100% activity compared to the CD3ζ intracellular T-cell signaling domain). In some aspects, the variants or homologs have at least 90%, 95%, 96%, 97%, 98%, 99% or 100% amino acid sequence identity across the whole sequence or a portion of the sequence (e.g. a 50, 100, 150 or 200 continuous amino acid portion) compared to a naturally occurring CD3ζ intracellular T-cell signaling domain polypeptide. In some cases, the CD3ζ intracellular T-cell signaling domain is a human CD3ζ intracellular T-cell signaling domain protein. In some cases, a variant or mutant of the CD3ζ intracellular T-cell signaling domain protein includes no more than 5, 4, 3, 2, or 1 deletions compared to the naturally occurring CD3ζ intracellular T-cell signaling domain protein. In some cases, a variant or mutant of the CD3ζ intracellular T-cell signaling domain protein includes no more than 5, 4, 3, 2, or 1 insertions compared to the naturally occurring CD3ζ intracellular T-cell signaling domain protein. In some cases, a variant or mutant of the CD3ζ intracellular T-cell signaling domain protein does not include deletions compared to the naturally occurring CD3ζ intracellular T-cell signaling domain protein. In some cases, a variant or mutant of the CD3ζ intracellular T-cell signaling domain protein does not include insertions compared to the naturally occurring CD3ζ intracellular T-cell signaling domain protein. In some cases, a variant or mutant of the CD3ζ intracellular T-cell signaling domain protein includes substitutions that are conservative substitutions compared to the naturally occurring CD3ζ intracellular T-cell signaling domain protein. In some cases, the CD3ζ intracellular T-cell signaling domain includes all or a portion of the protein identified by the NCBI sequence reference NP_000725.1, or an isoform or naturally occurring mutant or variant thereof. In some cases, the CD3ζ intracellular T-cell signaling domain includes all or a portion of the protein identified by the NCBI sequence reference NP_932170.1, or an isoform or naturally occurring mutant or variant thereof. Non-limiting examples of human CD3-zeta amino acid sequences available under NCBI sequence references are identified supra. In some cases, the CD3ζ intracellular T-cell signaling domain is encoded by all or a portion of the nucleic acid sequence identified by the NCBI sequence reference NM_000734.3, or an isoform or naturally occurring mutant or variant thereof. In some cases, the CD3ζ intracellular T-cell signaling domain is encoded by all or a portion of the nucleic acid sequence identified by the NCBI sequence reference NM_198053.2, or an isoform or naturally occurring mutant or variant thereof. In some cases, a variant or mutant of the CD3ζ intracellular T-cell signaling domain nucleic acid sequence includes no more than 5, 4, 3, 2, or 1 deletions compared to the naturally occurring CD3ζ intracellular T-cell signaling domain nucleic acid sequence. In some cases, a variant or mutant of the CD3ζ intracellular T-cell signaling domain nucleic acid sequence includes no more than 5, 4, 3, 2, or 1 insertions compared to the naturally occurring CD3ζ intracellular T-cell signaling domain nucleic acid sequence. In some cases, a variant or mutant of the CD3ζ intracellular T-cell signaling domain nucleic acid sequence does not include deletions compared to the naturally occurring CD3ζ intracellular T-cell signaling domain nucleic acid sequence. In some cases, a variant or mutant of the CD3ζ intracellular T-cell signaling domain nucleic acid sequence does not include insertions compared to the naturally occurring CD3ζ intracellular T-cell signaling domain nucleic acid sequence. In some cases, a variant or mutant of the CD3ζ intracellular T-cell signaling domain nucleic acid sequence includes substitutions that are conservative substitutions compared to the naturally occurring CD3ζ intracellular T-cell signaling domain nucleic acid sequence.

[0133] The phrase "specifically (or selectively) binds to an antibody" or "specifically (or selectively) immunoreactive with," when referring to a protein or peptide refers to a binding reaction that is determinative of the presence of the protein, often in a heterogeneous population of proteins and other biologics. Thus, under designated immunoassay conditions, the specified antibodies bind to a particular protein at least two times the background and more typically more than 10 to 100 times background. Specific binding to an antibody under such conditions typically requires an antibody that is selected for its specificity for a particular protein. For example, polyclonal antibodies can be selected to obtain only a subset of antibodies that are specifically immunoreactive with the selected antigen and not with other proteins. This selection may be achieved by subtracting out antibodies that cross-react with other molecules. A variety of immunoassay formats may be used to select antibodies specifically immunoreactive with a particular protein. For example, solid-phase ELISA immunoassays are routinely used to select antibodies specifically immunoreactive with a protein (see, e.g., Harlow & Lane, Using Antibodies, A Laboratory Manual (1998) for a description of immunoassay formats and conditions that can be used to determine specific immunoreactivity).

[0134] A "ligand" refers to an agent, e.g., a polypeptide or other molecule, capable of binding to a receptor.

[0135] The term "recombinant" when used with reference, for example, to a cell, a nucleic acid, a protein, or a vector, indicates that the cell, nucleic acid, protein or vector has been modified by or is the result of laboratory methods. Thus, for example, recombinant proteins include proteins

produced by laboratory methods. Recombinant proteins can include amino acid residues not found within the native (non-recombinant) form of the protein or can be include amino acid residues that have been modified, e.g., labeled.

[0136] The term "heterologous" when used with reference to portions of a nucleic acid indicates that the nucleic acid comprises two or more subsequences that are not found in the same relationship to each other in nature. For instance, the nucleic acid is typically recombinantly produced, having two or more sequences from unrelated genes arranged to make a new functional nucleic acid, e.g., a promoter from one source and a coding region from another source. Similarly, a heterologous protein indicates that the protein comprises two or more subsequences that are not found in the same relationship to each other in nature (e.g., a fusion protein).

[0137] A "cell" as used herein, refers to a cell carrying out metabolic or other functions sufficient to preserve or replicate its genomic DNA. A cell can be identified by well-known methods in the art including, for example, presence of an intact membrane, staining by a particular dye, ability to produce progeny or, in the case of a gamete, ability to combine with a second gamete to produce a viable offspring. Cells may include prokaryotic and eukaryotic cells. Prokaryotic cells include but are not limited to bacteria. Eukaryotic cells include but are not limited to yeast cells and cells derived from plants and animals, for example mammalian (e.g., human) and insect (e.g., *spodoptera*) cells. Cells may be useful when they are naturally nonadherent or have been treated not to adhere to surfaces, for example by trypsinization.

[0138] The word "expression" or "expressed" as used herein in reference to a gene means the transcriptional and/or translational product of that gene. The level of expression of a DNA molecule in a cell may be determined on the basis of either the amount of corresponding mRNA that is present within the cell or the amount of protein encoded by that DNA produced by the cell. The level of expression of non-coding nucleic acid molecules (e.g., siRNA) may be detected by standard PCR or Northern blot methods well known in the art. See, Sambrook et al., 1989 *Molecular Cloning: A Laboratory Manual,* 18.1-18.88.

[0139] The terms "plasmid", "vector" or "expression vector" refer to a nucleic acid molecule that encodes for genes and/or regulatory elements necessary for the expression of genes. Expression of a gene from a plasmid can occur in cis or in trans. If a gene is expressed in cis, the gene and the regulatory elements are encoded by the same plasmid. Expression in trans refers to the instance where the gene and the regulatory elements are encoded by separate plasmids.

[0140] The terms "transfection", "transduction", "transfecting" or "transducing" can be used interchangeably and are defined as a process of introducing a nucleic acid molecule or a protein to a cell. Nucleic acids are introduced to a cell using non-viral or viral-based methods. The nucleic acid molecules may be gene sequences encoding complete proteins or functional portions thereof. Non-viral methods of transfection include any appropriate transfection method that does not use viral DNA or viral particles as a delivery system to introduce the nucleic acid molecule into the cell. Exemplary non-viral transfection methods include calcium phosphate transfection, liposomal transfection, nucleofection, sonoporation, transfection through heat shock, magnetifection and electroporation. In some embodiments, the nucleic acid molecules are introduced into a cell using electroporation following standard procedures well known in the art. For viral-based methods of transfection any useful viral vector may be used in the methods described herein. Examples for viral vectors include, but are not limited to retroviral, adenoviral, lentiviral and adeno-associated viral vectors. In some embodiments, the nucleic acid molecules are introduced into a cell using a retroviral vector following standard procedures well known in the art. The terms "transfection" or "transduction" also refer to introducing proteins into a cell from the external environment. Typically, transduction or transfection of a protein relies on attachment of a peptide or protein capable of crossing the cell membrane to the protein of interest. See, e.g., Ford et al. (2001) *Gene Therapy* 8:1-4 and Prochiantz (2007) *Nat. Methods* 4:119-20.

[0141] Expression of a transfected gene can occur transiently or stably in a cell. During "transient expression" the transfected gene is not transferred to the daughter cell during cell division. Since its expression is restricted to the transfected cell, expression of the gene is lost over time. In contrast, stable expression of a transfected gene can occur when the gene is co-transfected with another gene that confers a selection advantage to the transfected cell. Such a selection advantage may be a resistance towards a certain toxin that is presented to the cell. Expression of a transfected gene can further be accomplished by transposon-mediated insertion into to the host genome. During transposon-mediated insertion, the gene is positioned in a predictable manner between two transposon linker sequences that allow insertion into the host genome as well as subsequent excision. Stable expression of a transfected gene can further be accomplished by infecting a cell with a lentiviral vector, which after infection forms part of (integrates into) the cellular genome thereby resulting in stable expression of the gene.

[0142] "Contacting" is used in accordance with its plain ordinary meaning and refers to the process of allowing at least two distinct species (e.g. chemical compounds including biomolecules or cells) to become sufficiently proximal to react, interact or physically touch. It should be appreciated, that the resulting reaction product can be produced directly from a reaction between the added reagents or from an intermediate from one or more of the added reagents which can be produced in the reaction mixture.

[0143] The term "modulation", "modulate", or "modulator" are used in accordance with their plain ordinary meaning and refer to the act of changing or varying one or more properties. "Modulator" refers to a composition that increases or decreases the level of a target molecule or the function of a target molecule or the physical state of the target of the molecule. "Modulation" refers to the process of changing or varying one or more properties. For example, as applied to the effects of a modulator on a biological target, to modulate means to change by increasing or decreasing a property or function of the biological target or the amount of the biological target.

[0144] As defined herein, the term "inhibition", "inhibit", "inhibiting" and the like in reference to a protein-inhibitor (e.g. antagonist) interaction means negatively affecting (e.g. decreasing) the activity or function of the protein relative to the activity or function of the protein in the absence of the inhibitor. In some cases, inhibition refers to reduction of a disease or symptoms of disease. Thus, In some cases,

inhibition includes, at least in part, partially or totally blocking stimulation, decreasing, preventing, or delaying activation, or inactivating, desensitizing, or down-regulating signal transduction or enzymatic activity or the amount of a protein. In some cases, the amount of inhibition may be 10%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, 90%, 100% or less in comparison to a control in the absence of the antagonist. In some cases, the inhibition is 1.5-fold, 2-fold, 3-fold, 4-fold, 5-fold, 10-fold, or more than the expression or activity in the absence of the antagonist.

[0145] Depending on context, the term "activation", "activate", "activating" and the like in reference to a protein-activator (e.g. agonist) interaction means positively affecting (e.g. increasing) the activity or function of the relative to the activity or function of the protein in the absence of the activator (e.g. composition described herein). Thus, In some cases, activation may include, at least in part, partially or totally increasing stimulation, increasing or enabling activation, or activating, sensitizing, or up-regulating signal transduction or enzymatic activity or the amount of a protein decreased in a disease. The amount of activation may be 10%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, 90%, I00% or more in comparison to a control in the absence of the agonist. In some cases, the activation is 1.5-fold, 2-fold, 3-fold, 4-fold, 5-fold, 10-fold, or more than the expression or activity in the absence of the agonist.

[0146] The term "aberrant" as used herein refers to different from normal. When used to describe enzymatic activity, aberrant refers to activity that is greater or less than a normal control or the average of normal non-diseased control samples. Aberrant activity may refer to an amount of activity that results in a disease, wherein returning the aberrant activity to a normal or non-disease-associated amount (e.g. by using a method as described herein), results in reduction of the disease or one or more disease symptoms.

[0147] Depending on context, the term "biological sample" or "sample" refers to a material or materials obtained from or derived from a subject or patient. In some cases, a biological sample includes sections of tissues such as biopsy and autopsy samples, and frozen sections taken for histological purposes. Non-limiting examples of samples include bodily fluids such as blood and blood fractions or products (e.g., serum, plasma, platelets, red blood cells, and the like), sputum, tissue, cultured cells (e.g., primary cultures, explants, and transformed cells) stool, urine, synovial fluid, joint tissue, synovial tissue, synoviocytes, fibroblast-like synoviocytes, macrophage-like synoviocytes, immune cells, hematopoietic cells, fibroblasts, macrophages, T cells, etc. A biological sample is typically obtained from a eukaryotic organism, such as a mammal such as a primate e.g., chimpanzee or human; cow; dog; cat; a rodent, e.g., guinea pig, rat, mouse; rabbit; or a bird; reptile; or fish. In some cases, a biological sample from the subject (e.g., such as blood) has aberrant CD6 expression and/or function compared to a control. In some cases, a biological sample from the subject (e.g., such as blood) has aberrant immune cell activity or growth (e.g., an abnormal number of CD6+ immune cells or CD6+ cells with abnormal activity).

[0148] A "control" sample or value refers to a sample that serves as a reference, usually a known reference, for comparison to a test sample. For example, a test sample can be taken from a test condition, e.g., in the presence of a test compound, and compared to samples from known conditions, e.g., in the absence of the test compound (negative control), or in the presence of a known compound (positive control). A control can also represent an average value gathered from a number of tests or results. One of skill in the art will recognize that controls can be designed for assessment of any number of parameters. For example, a control can be devised to compare therapeutic benefit based on pharmacological data (e.g., half-life) or therapeutic measures (e.g., comparison of side effects). One of skill in the art will understand which controls are valuable in a given situation and be able to analyze data based on comparisons to control values. Controls are also valuable for determining the significance of data. For example, if values for a given parameter are widely variant in controls, variation in test samples will not be considered as significant.

[0149] "Patient" or "subject in need thereof" refers to a living member of the animal kingdom suffering from or that may suffer from the indicated disorder. In some cases, the subject is a member of a species that includes individuals who naturally suffer from the disease. In some cases, a subject is a living organism suffering from or prone to a disease or condition that can be treated by administration of a composition or pharmaceutical composition as provided herein. Non-limiting examples include humans, other mammals, bovines, rats, mice, dogs, monkeys, goat, sheep, cows, deer, and other non-mammalian animals. In some embodiments, a patient is human.

[0150] The terms "disease" or "condition" refer to a state of being or health status of a patient or subject capable of being treated with a compound, pharmaceutical composition, or method provided herein. In some cases, the disease is an autoimmune disease (e.g., Type I Diabetes, Graft-versus-Host Disease). In some cases,

[0151] An "autoimmune disease" as used herein refers to a disease or disorder that arises from altered immune reactions by the immune system of a subject, e.g., against substances tissues and/or cells normally present in the body of the subject. Autoimmune diseases include, but are not limited to, arthritis, rheumatoid arthritis, psoriatic arthritis, juvenile idiopathic arthritis, scleroderma, systemic scleroderma, multiple sclerosis, systemic lupus erythematosus (SLE), myasthenia gravis, juvenile onset diabetes, diabetes mellitus type 1, Guillain-Barre syndrome, Hashimoto's encephalitis, Hashimoto's thyroiditis, ankylosing spondylitis, psoriasis, Sjogren's syndrome, vasculitis, glomerulonephritis, auto-immune thyroiditis, Behcet's disease, Crohn's disease, ulcerative colitis, bullous pemphigoid, sarcoidosis, psoriasis, ichthyosis, Graves ophthalmopathy, inflammatory bowel disease, Addison's disease, Vitiligo, asthma, Graft-versus-Host Disease, and allergic asthma.

[0152] As used herein, an "inflammatory disease" refers to a disease or disorder associated with abnormal or altered inflammation. Inflammation is a biological response initiated by the immune system as part of the healing process in response to a pathogen, damaged cells or tissues or irritants. Chronic inflammation can lead to a variety of diseases. Inflammatory diseases include, but are not limited to, atherosclerosis, allergies, asthma, rheumatoid arthritis, transplant rejection, celiac disease, chronic prostatitis, inflammatory bowel diseases, pelvic inflammatory diseases, and inflammatory myopathies.

[0153] The term "associated" or "associated with" in the context of a substance or substance activity or function associated with a disease (e.g., an autoimmune disease) means that the disease is caused by (in whole or in part), or

a symptom of the disease is caused by (in whole or in part) the substance or substance activity or function.

[0154] The terms "treating", or "treatment" refers to any indicia of success in the treatment or amelioration of an injury, disease, pathology or condition, including any objective or subjective parameter such as abatement; remission; diminishing of symptoms or making the injury, pathology or condition more tolerable to the patient; slowing in the rate of degeneration or decline; making the final point of degeneration less debilitating; improving a patient's physical or mental well-being. The treatment or amelioration of symptoms can be based on objective or subjective parameters; including the results of a physical examination, neuropsychiatric exams, and/or a psychiatric evaluation. The term "treating" and conjugations thereof, include prevention of an injury, pathology, condition, or disease. In some cases, "treating" refers to treatment of an autoimmune disease.

[0155] An "effective amount" or "therapeutically effective amount" is an amount sufficient for a compound to accomplish a stated purpose relative to the absence of the compound (e.g. achieve the effect for which it is administered, treat a disease, reduce enzyme activity, increase enzyme activity, reduce a signaling pathway, or reduce one or more symptoms of a disease or condition). An example of an "effective amount" is an amount sufficient to contribute to the treatment, prevention, or reduction of a symptom of a disease, which could also be referred to as a "therapeutically effective amount." A "reduction" of a symptom or symptoms (and grammatical equivalents of this phrase) means decreasing of the severity or frequency of the symptom(s), or elimination of the symptom(s). The exact amounts will depend on the purpose of the treatment, and will be ascertainable by one skilled in the art using known techniques (see, e.g., Lieberman, *Pharmaceutical Dosage Forms* (vols. 1-3, 1992); Lloyd, *The Art, Science and Technology of Pharmaceutical Compounding* (1999); Pickar, *Dosage Calculations* (1999); and *Remington: The Science and Practice of Pharmacy,* 20th Edition, 2003, Gennaro, Ed., Lippincott, Williams & Wilkins).

[0156] "Pharmaceutically acceptable excipient" and "pharmaceutically acceptable carrier" refer to a substance that aids the administration of an active agent to and absorption by a subject and can be included in the compositions of the present invention without causing a significant adverse toxicological effect on the patient. Non-limiting examples of pharmaceutically acceptable excipients include water, NaCl, normal saline solutions, lactated Ringer's, normal sucrose, normal glucose, binders, fillers, disintegrants, lubricants, coatings, sweeteners, flavors, salt solutions (such as Ringer's solution), alcohols, oils, gelatins, carbohydrates such as lactose, amylose or starch, fatty acid esters, hydroxymethycellulose, polyvinyl pyrrolidine, and colors, and the like. Such preparations can be sterilized and, if desired, mixed with auxiliary agents such as lubricants, preservatives, stabilizers, wetting agents, emulsifiers, salts for influencing osmotic pressure, buffers, coloring, and/or aromatic substances, and the like, that do not deleteriously react with the compounds of the invention. One of skill in the art will recognize that other pharmaceutical excipients are useful in the present invention.

[0157] The term "preparation" is intended to include the formulation of the active compound with encapsulating material as a carrier providing a capsule in which the active component with or without other carriers, is surrounded by a carrier, which is thus in association with it. Similarly, cachets and lozenges are included. Tablets, powders, capsules, pills, cachets, and lozenges can be used as solid dosage forms suitable for oral administration.

[0158] In some cases, the term "administering" includes oral administration, administration as a suppository, topical contact, intravenous, parenteral, intraperitoneal, intramuscular, intralesional, intrathecal, intranasal or subcutaneous administration, or the implantation of a slow-release device, e.g., a mini-osmotic pump, to a subject. In some cases, administration is by any route, including parenteral and transmucosal (e.g., buccal, sublingual, palatal, gingival, nasal, vaginal, rectal, or transdermal). Parenteral administration includes, e.g., intravenous, intramuscular, intra-arteriole, intradermal, subcutaneous, intraperitoneal, intraventricular, and intracranial. Other modes of delivery include, but are not limited to, the use of liposomal formulations, intravenous infusion, transdermal patches, etc.

[0159] Pharmaceutical compositions may include compositions wherein the active ingredient (e.g. compounds described herein, including embodiments or examples) is contained in a therapeutically effective amount, i.e., in an amount effective to achieve its intended purpose. The actual amount effective for a particular application will depend, inter alia, on the condition being treated. When administered in methods to treat a disease, such compositions will contain an amount of active ingredient effective to achieve the desired result, e.g., modulating the activity of a target molecule, and/or reducing, eliminating, or slowing the progression of disease symptoms.

Recombinant Proteins and CAR T-Cells

[0160] In an aspect, provided herein are recombinant proteins including the proteins expressed by the isolated nucleic acid provided herein, including embodiments thereof. Thus, in an aspect is provided a recombinant protein, such as a chimeric antigen receptor (CAR), that includes a single chain variable fragment (scFv) targeted to CD6 and a transmembrane domain. In an aspect, provided herein is a scFv targeted to CD6 without a transmembrane domain. In an aspect, provided herein is a cell (e.g., a population of cells, such as a population of immune effector cells) engineered to express a CAR, wherein the CAR comprises an antigen-binding domain, and a transmembrane domain. In some cases, the antigen binding domain comprises an antibody fragment or variant targeted to CD6. In some cases, the antigen-binding domain is a single chain variable fragment (scFv) targeted to CD6. In some cases, the CAR further comprises an intracellular signaling domain. In some cases, the cell that expresses the CAR is a T lymphocyte (a CAR T-cell) or an NK cell. In some cases, the cell that expresses the CAR is a T lymphocyte (a CAR T-cell) or an NK cell. In some cases, the cell is a CD4+ T cell, or a CD8+ T cell. In some cases, the T-cell is a regulatory T-cell (Treg).

[0161] In some cases, the antigen-binding domain can comprise CDRs of a monoclonal antibody, variable regions of a monoclonal antibody, and/or antigen binding fragments thereof. In some cases, the fragment can be any number of different antigen binding domains of an antigen-specific antibody. In some cases, the antigen-binding domain comprises a CD6-binding fragment of an anti-CD6 antibody. In some cases, the antigen-binding domain comprises the CDRs of an anti-CD6 antibody. In some cases, the antigen-

binding domain comprises the VH and VL chains of an anti-CD6 antibody. In some cases, the antigen-binding domain comprises a scFv that comprises CDRs of an anti-CD6 antibody. In some cases, the antigen-binding domain comprises a scFv that comprises the VH and VL chains of an anti-CD6 antibody. In some cases, the anti-CD6 antibody is a monoclonal antibody. In some cases, the monoclonal antibody is a human or a humanized monoclonal antibody. In some cases, the monoclonal antibody is itolizumab. In some cases, the fragment is an antigen-specific scFv encoded by a sequence that is optimized for human codon usage for expression in human cells. In some cases, the monoclonal antibody is a chimericmonoclonal antibody. In some cases, the monoclonal antibody is itolizumab. In some cases, the monoclonal antibody is T12. 1. In some cases, the monoclonal antibody is UMCD6. In some cases, the monoclonal antibody is MEM98. In some cases, the monoclonal antibody is MT605. In some cases, the monoclonal antibody is an antibody described in Gangemi et al. (1989) *J Immunol* 143(8):2439-47 or U.S. Pat. No. 6,572,857, the entire contents of each of which are incorporated herein by reference. In some cases, the fragment is an antigen-specific scFv encoded by a sequence that is optimized for human codon usage for expression in human cells. In some cases, the antigen-binding domain includes the following VH sequence or a variant thereof:

(SEQ ID NO: 35)
EVQLVESGGGLVKPGGSLKLSCAASGFKFSRYAMSWVRQAPGKRLEWVAT

ISSGGSYIYYPDSVKGRFTISRDNVKNTLYLQMSSLRSEDTAMYYCARRD

YDLDYFDSWGQGTLVTVSS.

In some cases, the antigen-binding domain includes the following VL sequence or a variant thereof:

(SEQ ID NO: 34)
DIQMTQSPSSLSASVGDRVTITCKASRDIRSYLTWYQQKPGKAPKTLIYY

ATSLADGVPSRF SGSGSGQDYSLTISSLESDDTATYYCLQHGESPFTFG

SGTKLEIKRA.

In some cases, the antigen-binding domain includes the following VH sequence or a variant thereof:

(SEQ ID NO: 68)
EVQLVESGGGLVKPGGSLKLSCAASGFKFSRYAMSWVRQTPEKRLEWVAT

ISSGGSYIYYPDSVKGRFTISRDNVKNTLYLQMSSLRSEDTAMYYCARRD

YDLDYFDSWGQGTTLTVSS.

In some cases, the antigen-binding domain includes the following VL sequence or a variant thereof:

(SEQ ID NO: 69)
DIKMTQSPSSMYASLGERVTITCKASRDIRSYLTWYQQKPWKSPKTLIY

YATSLADGVPSRF SGSGSGQDYSLTISSLESDDTATYYCLQHGESPFT

FGSGTKLEIKRA.

In some cases, the VL includes the following sequence or a variant thereof:

(SEQ ID NO: 75)
IQMTQSPSSLSASVGDRVTITCKASRDIRSYLTWYQQKPGKAPKTLIYY

ATSLADGVPSRFSGSGSGQ.

In some cases, the VL includes the following sequence or a variant thereof:

(SEQ ID NO: 76)
DIQMTQSPSSLSASVGDRVTITCKASRDIRSY.

In some cases, the VL includes the following sequence or a variant thereof:

(SEQ ID NO: 77)
LTWYQQKPGKAPKTLIYYATSLADGVPSRFSGSGSGQDYSLTISSLESDD

TATYYCLQHGESPFT.

In some cases, the VL includes the following sequence or a thereof: FGSGTKLEIKRA (SEQ ID NO:78). In some cases, the VH includes the following sequence or a variant thereof:

(SEQ ID NO: 79)
EVQLVESGGGLVKPGGSLKLSCAASGFKFSRYAMS.

In some cases, the VH includes the following sequence or a variant thereof: WVRQAPGKRLEWVATISSGG (SEQ ID NO:80). In some cases, the VH includes the following sequence or a variant thereof:

(SEQ ID NO: 81)
SYIYYPDSVKGRFTISRDNVKNTLYLQMSSLRSEDTAMYYCARRDYDLDY

FDS.

In some cases, the VH includes the following sequence or a variant thereof: WGQGTLVTVSS (SEQ ID NO:82). In some cases, a variant of a VH or VL sequence provided herein has 5, 4, 3, 2, 1, or 0 deletions compared to the sequence. In some cases, a variant of a VH or VL sequence provided herein has 5, 4, 3, 2, 1, or 0 insertions compared to these sequences. In some cases, a variant of a VH or VL sequence provided herein has 5, 4, 3, 2, 1, or 0 substitutions compared to the sequence. In some embodiments, a variant of a VH or VL sequence provided herein has 10, 9, 8, 7, 6, 5, 4, 3, 2, or 1 substitutions compared to the sequence. In some cases, 1 or more or all of the substitutions are conservative substitutions.

[0162] In various embodiments, the chimeric antigen receptor comprises: a IL-13 (e.g., an IL-13 comprising the amino acid sequence GPVPPSTAL-RYLIEELVNITQNQKAPLCNGSMVWSINLTAGMY-CAALESLINVSGCSAIE KTQRMLSGFCPHKVSAGQFSSLHVRDTKI-EVAQFVKDLLLHLKKLFREGRFN (SEQ ID NO:101) or variant thereof with 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10 single amino acid substitutions). In some embodiments, the CAR comprises: a variant of a human IL13 having 1-10 amino acid modification that increase binding specificity for IL13Rα2 versus IL13Rα1 (e.g. E13Y).

[0163] In some embodiments, a CD19-targeted CAR (CD19 CAR, also called anti-CD19 CAR herein) described herein include a CD19 targeting scFv (e.g., an scFv comprising the amino acid sequence:

(SEQ ID NO: 102)
DIQMTQTTSSLSASLGDRVTISCRASQDISKYLNWYQQKPDGTVKLLIYH

TSRLHSGVPSRFSGSGSGTDYSLTISNLEQEDIATYFCQQGNTLPYTFGG

GTKLEITGSTSGSGKPGSGEGSTKGEVKLQESGPGLVAPSQSLSVTCTVS

GVSLPDYGVSWIRQPPRKGLEWLGVIWGSETTYYNSALKSRLTIIKDNSK

SQVFLKMNSLQTDDTAIYYCAKHYYYGGSYAMDYWGQGTSVTVSS

or variant thereof with 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10 single amino acid substitutions or comprising the sequence DIQMTQTTSSLSASLGDRVTISCRASQDISKY-LNWYQQKPDGTVKLLIYHTSRLHSGVPS RFSGSGSGTDYSLTISNLEQEDIATYFCQQGNTLPYTF (SEQ ID NO:103) or variant thereof with 1, 2, 3, 4, or 5 single amino acid substitutions and the sequence TKLEITGSTSGSGKPGSGEGSTK-GEVKLQESGPGLVAP-SQSLSVTCTVSGVSLPDYGVSW IRQPPRKGLEW-LGVIWGSETTYYNSALKSRLTIIKDNSKSQVFLKMNS LQTDDTAIYYCA KHYYYGGSYAMDYWGQGTSVTVSS (SEQ ID NO:104) or variant thereof with 1, 2, 3, 4, or 5 single amino acid substitutions joined by a flexible linker.

[0164] In some embodiments, a CD6-targeted CAR (CD6 CAR, also called anti-CD6 CAR herein) described herein include a CD6 targeting scFv (e.g., an scFv comprising the amino acid sequence:

(SEQ ID NO: 105)
EVQLVESGGGLVKPGGSLKLSCAASGFKFSRYAMSWVRQAPGKRLEWVAT

ISSGGSYIYYPDSVKGRFTISRDNVKNTLYLQMSSLRSEDTAMYYCARRD

YDLDYFDSWGQGTLVTVSSGSTSGGGSGGGSGGGGSSDIQMTQSPSSLSA

SVGDRVTITCKASRDIRSYLTWYQQKPGKAPKTLIYYATSLADGVPSRFS

GSGSGQDYSLTISSLESDDTATYYCLQHGESPFTFGSGTKLEIKRA

or variant thereof with 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10 single amino acid substitutions or comprising the sequence EVQLVESGGGLVKPGGSLKLSCAASGFKFSRYAM-SWVRQAPGKRLEWVATISSGGSYI YYPDSVKGRFTISRDNVKNTLYLQMSSLRSED-TAMYYCARRDYDLDYFDSWGQGTLV TV (SEQ ID NO:106) or variant thereof with 1, 2, 3, 4, or 5 single amino acid substitutions and the sequence

(SEQ ID NO: 107)
DIQMTQSPSSLSASVGDRVTITCKASRDIRSYLTWYQQKPGKAPKTLIYY

ATSLADGVPSRFSGSGSGQDYSLTISSLESDDTATYYCLQHGESPFTFGS

GTKLEIKRA

or variant thereof with 1, 2, 3, 4, or 5 single amino acid substitutions joined by a flexible linker.

[0165] In some embodiments, a CD6-targeted CAR (CD6 CAR, also called anti-CD6 CAR herein) described herein include a CD6 targeting scFv (e.g., an scFv comprising the amino acid sequence:

(SEQ ID NO: 108)
EVQLVESGGGLVKPGGSLKLSCAASGFKFSRYAMSWVRQAPGKGLEWVAT

ISSGGSYIYYPDSVKGRFTISRDNVKNTLYLQMSSLRSEDTAMYYCARRD

YDLDYFDSWGQGTLVTVSSGSTSGGGSGGGSGGGGSGDIQMTQSPSSLSA

SVGDRVTITCKASRDIRSYLTWYQQKPGKAPKTLIYYATSLADGVPSRFS

GSGSGQDYSLTISSLESDDTATYYCLQHGESPFTFGSGTKMEIKRA

or variant thereof with 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10 single amino acid substitutions or comprising the sequence EVQLVESGGGLVKPGGSLKLSCAASGFKFSRYAM-SWVRQAPGKGLEWVATISSGGSYI YYPDSVKGRFTISRDNVKNTLYLQMSSLRSED-TAMYYCARRDYDLDYFDSWGQGTLV TVSS (SEQ ID NO:109) or variant thereof with 1, 2, 3, 4, or 5 single amino acid substitutions and the sequence

(SEO ID NO: 110)
DIQMTQSPSSLSASVGDRVTITCKASRDIRSYLTWYQQKPGKAPKTLIYY

ATSLADGVPSRFSGSGSGODYSLTISSLESDDTATYYCLOHGESPFTFGS

GTKMEIKRA

or variant thereof with 1, 2, 3, 4, or 5 single amino acid substitutions joined by a flexible linker.

[0166] In some embodiments, a CD6-targeted CAR (CD6 CAR, also called anti-CD6 CAR herein) described herein include a CD6 targeting scFv (e.g., an scFv comprising the amino acid sequence: DIQMTQSPSSL-SASVGDRVTITCKASRDIR-SYLTWYQQKPGKAPKTLIYYATSLADGVPS RFSGSGSGQDYSLTISSLESDDTATYY-CLQHGESPFTFGSGTKLEIKRAGSTSGGGSGGGS GGGGSSEVQLVESGGGLVKPGGSLKLS-CAASGFKFSRYAMSWVRQAPGKRLEWVATIS SGGSYIYYPDSVKGRFTISRDNVKNT-LYLQMSSLRSEDTAMYYCARRDYDLDYFDSWG QGTLVTVSS (SEQ ID NO:111) or variant thereof with 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10 single amino acid substitutions or comprising the sequence

(SEQ ID NO: 112)
DIQMTQSPSSLSASVGDRVTITCKASRDIRSYLTWYQQKPGKAPKTLIYY

ATSLADGVPSRFSGSGSGQDYSLTISSLESDDTATYYCLQHGESPFTFGS

GTKMEIKRA

or variant thereof with 1, 2, 3, 4, or 5 single amino acid substitutions and the sequence EVQLVESGG-GLVKPGGSLKLSCAASGFKFSRYAMSWVRQAPGK-GLEWVATISSGGSYI YYPDSVKGRFTISRDNVKNT-LYLQMSSLRSEDTAMYYCARRDYDLDYFDSWGQG TLV TVSS (SEQ ID NO:113) or variant thereof with 1, 2, 3, 4, or 5 single amino acid substitutions joined by a flexible linker.

TABLE 1

Exemplary Sequences for Antigen Binding domains and light and heavy chain variable regions.

Heavy CDR1 Kabat	VQLVESGGGLVKPGGSLKLS
Heavy CDR2 Kabat	FSRYAMSWVRQAPGK
Heavy CDR3 Kabat	RDYDLDYFDSWGQGTLVTV
Heavy Chain Variable Region	EVQLVESGGGLVKPGGSLKLSCAASGFKFSRYAM SWVRQAPGKRLEWVATISSGGSYIYYPDSVKGRF TISRDNVKNTLYLQMSSLRSEDTAMYYCARRDYD LDYFDSWGQGTLVTVSS
Light Chain Variable Region	DIQMTQSPSSLSASVGDRVTITCKASRDIRSYLT WYQQKPGKAPKTLIYYATSLADGVPSRFSGSGSG QDYSLTISSLESDDTATYYCLQHGESPFTFGSGT KLEIKRA
Portion of Light Chain Variable Region	IQMTQSPSSLSASVGDRVTITCKASRDIRSYLTW YQQKPGKAPKTLIYYATSLADGVPSRFSGSGSGQ

[0167] In some cases, the antigen-binding domain (e.g., an scFv that is part of the CAR) has a relatively low affinity (K_D) for CD6, CD19 or an IL-13R, while still being specific for CD6, CD19, or an IL-13R. In some cases, the affinity is about 1×10^{-4}M to about 1×10^{-6}M, about 1×10^{-8} M to about 1×10^{-7} M, about 1×10^{-8} M to about 1×10^{-6} M, about 1×10^{-9} M to about 1×10^{-7} M, about 1.5×10^{-8}M to about 1.5×10^{-7}M, or about 1×10^{-7} M, 2×10^{-7}M, 3×10^{-7}M, 4×10^{-7}M, 5×10^{-7}M, 6×10^{-7}M, 7×10^{-7}M, 8×10^{-7}M, 9×10^{-7} M, about 1×10^{-8}M, 2×10^{-8}M, 3×10^{-8}M, 4×10^{-8} M, 5×10^{-8} M, 6×10^{-8} M, 7×10^{-8} M, 8×10^{-8} M, or 9×10^{-8} M. One of skill in the art can readily detect the K_D of an antibody. In a non-limiting example, affinity may be detected, e.g., by yeast surface display. This approach is a genotype-phenotype linkage strategy mediated by production, secretion, and capture of protein candidates. Candidate proteins can be sorted using combinations of multiple strategies with multiple selection pressures including affinity and stability. See, e.g., Feldhaus et al. (2003) Flow-cytometric isolation of human antibodies from a nonimmune *Saccharomyces cerevisiae* surface display library. Nature biotechnology. 21:163-170; and Zoriak et al. (207) Yeast display biopanning identifies human antibodies targeting glioblastoma stem-like cells. Scientific Reports. 7:15840, the entire contents of each of which are incorporated herein by reference.

[0168] In some cases, an scFv may be designed to have a particular orientation (e.g., V_H-V_L or V_L-V_H from the N-terminus to the C-terminus). In some cases, the V_H and V_L in an scFv are oriented V_H-V_L from the N-terminus to the C-terminus. In some cases, the V_H and V_L in an scFv are oriented V_L-V_H from the N-terminus to the C-terminus. In some cases, the V_H and V_L portions of the expressed protein will have a slightly different conformation depending on the orientation thereof. In some cases, the orientation of the V_H and V_L relationship may confer differential affinities for the ligand (e.g., CD6). In some cases, the differential affinity of one orientation compared to another is one order of magnitude or higher.

[0169] In some cases, the V_H and V_L portions of the scFv are directly adjacent and contiguous to one another. Alternatively, the V_H and V_L of the scFv may be separated by a linker (e.g., flexible linker). In some cases, the linker is a polypeptide linker. In some cases, the polypeptide linker is a flexible linker. In some cases, the V_H and V_L (in either orientation) of the scFv may be fused through a flexible linker with different sizes e.g.: 18 amino acids, 19 amino acids, or 20 amino acids; allowing the V_H and V_L of the scFv to fold into their native configuration and conserving the antigen-binding properties. In some cases, the linker includes glycine and/or serine residues. In some cases, the linker has the amino acid sequence GST-SGGGSGGGSGGGGSS (SEQ ID NO:36). In some cases, the linker has the amino acid sequence GGGGSGGGGSGGGGSGGGGS (SEQ ID NO:37). In some cases, the linker is about 18 amino acids in length. In some cases, the linker is 18 amino acids in length. In some cases, the linker is about 19 amino acids in length. In some cases, the linker is 19 amino acids in length. In some cases, the linker is about 20 amino acids in length. In some cases, the linker is 20 amino acids in length. In some cases, the linker sequence is long enough to allow the expressed scFv to fold into its native configuration. In some cases, the linker sequence is long enough to allow the expressed scFv to maintain its antigen-binding properties. Techniques for assessing protein folding include, but are not limited to, NMR, X-Ray crystallography, circular dichroism, fluorescence spectroscopy, dual polarization interferometry, and other techniques well known in the art. Techniques for assessing antigen-binding behavior include, but are not limited to, surface plasm on resonance (SPR), various ligand binding assays, and other techniques well known in the art.

[0170] In some cases, a recombinant protein provided herein, including embodiments thereof, may further include additional components of a CAR. CARs that include such additional components and cells expressing such CARs are also included.

[0171] In some cases, the recombinant protein (such as a CAR) provided herein (e.g. isolated or expressed on the surface of a cell), including embodiments thereof, may further include a transmembrane domain as described herein, including embodiments thereof, a hinge region as described herein, including embodiments thereof, an intracellular signaling domain (such as a T-cell signaling domain) as described herein, including embodiments thereof, and/or a co-stimulatory domain as described herein, including embodiments thereof.

[0172] In some cases, an scFv or targeting domain as provided herein may be directly connected (e.g., covalently bound) to a transmembrane domain or may be connected (e.g., covalently bound) to the transmembrane domain through a hinge region.

[0173] A "hinge region" as provided herein is a polypeptide connecting an antigen-binding site domain (i.e., scFv) to a transmembrane domain. Any hinge region capable of connecting an scFv to a transmembrane domain is contemplated herein. In some cases, the hinge region is a polypeptide hinge region. In some cases, the polypeptide hinge region is a flexible hinge region. In some cases, the hinge region includes glycine and/or serine residues. In some

cases, the hinge region is or includes an antibody hinge region or a portion thereof. In some cases, the hinge region includes an antibody Fc domain or a portion thereof (e.g., a portion comprising a hinge region). Non-limiting examples of suitable hinge regions contemplated herein include a IgG Fc, human IgG Fc, human IgG1 Fc, IgG4 Fc, and human IgG4 Fc, or a portion thereof (i.e., a portion thereof that includes the hinge region). In some cases, the hinge region is an IgG Fc or a portion thereof. In some cases, the hinge region is a human IgG Fc or a portion thereof. In some cases, the hinge region is an IgG1 Fc or a portion thereof. In some cases, the hinge region is a human IgG1 Fc, or a portion thereof. In some cases, the hinge region is an IgG4 Fc, or a portion thereof. In some cases, the hinge regions is an human IgG4 Fc, or a portion thereof. In some cases, a IgG Fc hinge is used to connect the binding site domain to the CAR backbone. In some cases, an IgG1 or IgG4 human Fc or a portion thereof comprising a hinge region include one or more mutations to reduce or prevent the binding to the corresponding Fc receptor. In some cases, an IgG1 or IgG4 human Fc or a portion thereof comprising a hinge region does not include a mutation to reduce or prevent the binding to the corresponding Fc receptor. In some cases, the length of a portion of a Fc domain can be of 229 amino acids, 129 amino acids, or less.

[0174] In some cases, the hinge region is about 229 amino acids in length. In some cases, the hinge region is 229 amino acids in length. In some cases, the hinge region is about 129 amino acids in length. In some cases, the hinge region is 129 amino acids in length. In some cases, the hinge region is between about 129 to about 229 amino acids in length. In some cases, the hinge region is less than about 229 amino acids in length. In some cases, the hinge region is less than 229 amino acids in length. In some cases, the hinge region is less than about 129 amino acids in length. In some cases, the hinge region is less than 129 amino acids in length. In some cases, the hinge region is at least 22 amino acids in length. In some cases, the hinge region is 22 amino acids in length. In some cases, the hinge region is about 25, 50, 75, 100, 125, 150, 175, 200, 225, or 250 amino acids in length. In some cases, the hinge region is about 25 amino acids in length. In some cases, the hinge region is about 50 amino acids in length. In some cases, the hinge region is about 75 amino acids in length. In some cases, the hinge region is about 100 amino acids in length. In some cases, the hinge region is about 125 amino acids in length. In some cases, the hinge region is about 150 amino acids in length. In some cases, the hinge region is about 175 amino acids in length. In some cases, the hinge region is about 200 amino acids in length. In some cases, the hinge region is about 225 amino acids in length. In some cases, the hinge region is about 250 amino acids in length. In some cases, the hinge region is 25 amino acids in length. In some cases, the hinge region is 50 amino acids in length. In some cases, the hinge region is 75 amino acids in length. In some cases, the hinge region is 100 amino acids in length. In some cases, the hinge region is 125 amino acids in length. In some cases, the hinge region is 150 amino acids in length. In some cases, the hinge region is 175 amino acids in length. In some cases, the hinge region is 200 amino acids in length. In some cases, the hinge region is 225 amino acids in length. In some cases, the hinge region is 250 amino acids in length.

[0175] In some cases, the hinge region is between about 22 to about 250 amino acids in length. In some cases, the hinge region is between about 25 to about 250 amino acids in length. In some cases, the hinge region is between about 50 to about 250 amino acids in length. In some cases, the hinge region is between about 75 to about 250 amino acids in length. In some cases, the hinge region is between about 100 to about 250 amino acids in length. In some cases, the hinge region is between about 125 to about 250 amino acids in length. In some cases, the hinge region is between about 150 to about 250 amino acids in length. In some cases, the hinge region is between about 175 to about 250 amino acids in length. In some cases, the hinge region is between about 200 to about 250 amino acids in length. In some cases, the hinge region is between about 225 to about 250 amino acids in length. In some cases, the hinge region is between about 22 to about 225 amino acids in length. In some cases, the hinge region is between about 22 to about 200 amino acids in length. In some cases, the hinge region is between about 22 to about 175 amino acids in length. In some cases, the hinge region is between about 22 to about 150 amino acids in length. In some cases, the hinge region is between about 22 to about 125 amino acids in length. In some cases, the hinge region is between about 22 to about 100 amino acids in length. In some cases, the hinge region is between about 22 to about 75 amino acids in length. In some cases, the hinge region is between about 22 to about 50 amino acids in length. In some cases, the hinge region is between about 22 to about 25 amino acids in length.

[0176] In some cases, the hinge region includes an Fc domain. In some cases, the hinge region includes an IgG Fc domain. In some cases, the hinge region is an IgG1 Fc or a fragment thereof. In some cases, the hinge region is a human IgG1 Fc or a fragment thereof. In some cases, the hinge region is an IgG4 Fc or a fragment thereof. In some cases, the hinge region is a human IgG4 Fc or a fragment thereof.

[0177] In some cases, the hinge region may be a mutated hinge region. In some cases, a mutated hinge region (e.g., Fc) may be useful, for example, to prevent the Fc from binding to its cognate Fc receptor. In some cases, the hinge region (e.g., IgG, human IgG Fc, IgG1 Fc, human IgG1 Fc, IgG4 Fc, human IgG4 Fc) includes no more than 5, 4, 3, 2, or 1 deletions. In some cases, the hinge region (e.g., IgG, human IgG Fc, IgG1 Fc, human IgG1 Fc, IgG4 Fc, human IgG4 Fc) includes no more than 5, 4, 3, 2, or 1 insertions. In some cases, the hinge region (e.g., IgG, human IgG Fc, IgG1 Fc, human IgG1 Fc, IgG4 Fc, human IgG4 Fc) does not include deletions. In some cases, the hinge region (e.g., IgG, human IgG Fc, IgG1 Fc, human IgG1 Fc, IgG4 Fc, human IgG4 Fc) does not include insertions. In some cases, the hinge region (e.g., IgG, human IgG Fc, IgG1 Fc, human IgG1 Fc, IgG4 Fc, human IgG4 Fc) includes substitutions that are conservative substitutions.

[0178] In some cases, a transmembrane domain as provided herein refers to a polypeptide forming part of (e.g., spanning) a biological membrane. In some cases, the transmembrane domain provided herein is capable of spanning a biological membrane (e.g., a cellular membrane) from one side of the membrane through to the other side of the membrane. In some cases, the transmembrane domain spans only a portion of the membrane, but is sufficient to anchor an antigen-binding domain to the membrane. In some cases, the transmembrane domain spans from the intracellular side to the extracellular side of a cellular membrane. In some cases, transmembrane domains may include non-polar, hydrophobic residues, which anchor the proteins provided

herein including embodiments thereof in a biological membrane (e.g., cellular membrane of a T cell). Any transmembrane domain capable of anchoring the proteins provided herein including embodiments thereof is contemplated. Non-limiting examples of transmembrane domains include the transmembrane domains of CD28, CD8, CD4, or CD3-zeta (CD3ζ).

[0179] In some cases, the transmembrane domain includes a CD4 transmembrane domain or a variant thereof, a CD8 transmembrane domain or a variant thereof, a CD28 transmembrane domain or a variant thereof, or a CD3ζ transmembrane domain or a variant thereof. In some cases, recombinant protein such as a CAR (e.g., a cell expressing a CAR) comprises an intracellular co-stimulatory domain and/or an intracellular T-cell signaling domain.

[0180] In some cases, the transmembrane domain includes a CD4 transmembrane domain or a variant thereof. In some cases, the transmembrane domain includes a CD8 transmembrane domain or a variant thereof. In some cases, the transmembrane domain includes a CD28 transmembrane domain or a variant thereof. In some cases, the transmembrane domain includes a CD3ζ transmembrane domain or a variant thereof.

[0181] In some cases, the transmembrane domain is covalently bound to a heavy chain variable region of the scFv. In some cases, the transmembrane domain is covalently bound to a light chain variable region of the scFv. In some cases, the transmembrane domain is covalently bound to a heavy chain variable region of the scFv though a hinge region. In some cases, the transmembrane domain is covalently bound to a light chain variable region of the scFv through a hinge region. In some cases, a recombinant protein provided herein (such as a CAR, e.g., on the surface of a cell) comprises, from the N-terminal end to the C-terminal end a V_H, a V_L, and a transmembrane domain. In some cases, a recombinant protein provided herein (such as a CAR, e.g., on the surface of a cell) comprises, from the N-terminal end to the C-terminal end a V_L, a V_H, and a transmembrane domain. In some cases, a recombinant protein provided herein (such as a CAR, e.g., on the surface of a cell) comprises, from the N-terminal end to the C-terminal end a V_H, a linker, a V_L, and a transmembrane domain. In some cases, a recombinant protein provided herein (such as a CAR, e.g., on the surface of a cell) comprises, from the N-terminal end to the C-terminal end a V_L, a linker, a V_H, and a transmembrane domain. In some cases, a recombinant protein provided herein (such as a CAR, e.g., on the surface of a cell) comprises, from the N-terminal end to the C-terminal end a V_H, a linker, a V_L, a hinge region, and a transmembrane domain. In some cases, a recombinant protein provided herein (such as a CAR, e.g., on the surface of a cell) comprises, from the N-terminal end to the C-terminal end a V_L, a linker, a V_H, a hinge region, and a transmembrane domain. The V_H, V_L, linker, hinge region, and transmembrane domain referred to in this paragraph, refer to those disclosed herein, including embodiments thereof.

[0182] In some cases, the antigen-binding domain (e.g., the scFv) includes the CDR sequences of itolizumab. In some cases, the CDRs include the amino acid sequences set forth by SEQ ID NOs:28, 29, 30, 31, 32, and 33. In some cases, the CDRs are the amino acid sequences set forth by SEQ ID NOs: 28, 29, 30, 31, 32, and 33. In some cases, the CDRs specifically bind CD6. In some cases, the CDRs specifically bind CD6 with an affinity from between about 1×10^{-6} to 1×10^{-8}. In some cases, the CDRs specifically bind CD6 with an affinity of equal to or less than about 1×10^{-6} or 1×10^{-7}.

[0183] An "intracellular co-stimulatory signaling domain," "co-stimulatory signaling domain," or "intracellular co-stimulatory domain" as provided herein includes amino acid sequences capable of providing co-stimulatory signaling in response to binding of an antigen to the antigen-binding domain of the recombinant protein (e.g. CAR) provided herein including embodiments thereof. In some cases, the signaling of the co-stimulatory signaling domain results in production of cytokines and proliferation of a cell (e.g., a T cell) expressing the recombinant protein (e.g., CAR).

[0184] In some cases, the co-stimulatory domain is a CD28 intracellular co-stimulatory domain or a variant thereof, a 4-1BB intracellular co-stimulatory domain or a variant thereof, an ICOS intracellular co-stimulatory signaling domain or a variant thereof, an OX-40 intracellular co-stimulatory signaling domain or a variant thereof, a CTLA-4 cytoplasmic domain or a variant thereof, a PD-1 intracellular co-stimulatory domain or a variant thereof, or a GITR co-stimulatory domain or a variant thereof. In some cases, the co-stimulatory domain is a CD28 intracellular co-stimulatory domain (SEQ ID NO:7 or 8) or a variant thereof. In some cases, a 4-1BB intracellular co-stimulatory domain (SEQ ID NO:14) or a variant thereof. In some cases, the co-stimulatory domain is an ICOS intracellular co-stimulatory signaling domain or a variant thereof. In some cases, the co-stimulatory domain is an OX-40 intracellular co-stimulatory signaling domain or a variant thereof. In some cases, the co-stimulatory domain is a CTLA-4 intracellular co-stimulatory domain (SEQ ID NO:17) or a variant thereof. In some cases, the co-stimulatory domain is a PD-1 intracellular co-stimulatory domain or a variant thereof. In some cases, the co-stimulatory domain is a GITR co-stimulatory domain or a variant thereof.

[0185] In some cases, a recombinant protein provided herein (such as a CAR, e.g., on the surface of a cell) comprises, from the N-terminal end to the C-terminal end a V_H, a V_L, a transmembrane domain, and a co-stimulatory domain. In some cases, a recombinant protein provided herein (such as a CAR, e.g., on the surface of a cell) comprises, from the N-terminal end to the C-terminal end a V_L, a V_H, a transmembrane domain, and a co-stimulatory domain. In some cases, a recombinant protein provided herein (such as a CAR, e.g., on the surface of a cell) comprises, from the N-terminal end to the C-terminal end a V_H, a linker, a V_L, a transmembrane domain, and a co-stimulatory domain. In some cases, a recombinant protein provided herein (such as a CAR, e.g., on the surface of a cell) comprises, from the N-terminal end to the C-terminal end a V_L, a linker, a V_H, a transmembrane domain, and a co-stimulatory domain. In some cases, a recombinant protein provided herein (such as a CAR, e.g., on the surface of a cell) comprises, from the N-terminal end to the C-terminal end a V_H, a linker, a V_L, a hinge region, a transmembrane domain, and a co-stimulatory domain. In some cases, a recombinant protein provided herein (such as a CAR, e.g., on the surface of a cell) comprises, from the N-terminal end to the C-terminal end a V_L, a linker, a V_H, a hinge region, a transmembrane domain, and a co-stimulatory domain. The V_H, V_L, linker, hinge region, transmembrane domain, and a

co-stimulatory domain referred to in this paragraph, refer to those disclosed herein, including embodiments thereof.

[0186] An "intracellular T-cell signaling domain" as provided herein includes amino acid sequences capable of providing primary signaling in response to binding of an antigen to the antigen-binding domain of the recombinant protein (e.g. CAR) provided herein including embodiments thereof, including embodiments thereof. In some cases, the signaling of the intracellular T-cell signaling domain results in activation of the T cell expressing the same. In some cases, the signaling of the intracellular T-cell signaling domain results in proliferation (cell division) of a cell (e.g., a T cell) expressing the recombinant protein (e.g., CAR). In some cases, the signaling of the intracellular T-cell signaling domain results in expression by the T cell of proteins known in the art to characteristic of activated T cell (e.g., CTLA-4, PD-1, CD28, CD69).

[0187] In some cases, the intracellular T-cell signaling domain is a CD3ζ intracellular T-cell signaling domain.

[0188] In some cases, a recombinant protein provided herein (such as a CAR, e.g., on the surface of a cell) comprises, from the N-terminal end to the C-terminal end a V_H, a V_L, a transmembrane domain, a co-stimulatory domain, and an intracellular T-cell signaling domain. In some cases, a recombinant protein provided herein (such as a CAR, e.g., on the surface of a cell) comprises, from the N-terminal end to the C-terminal end a V_L, a V_H, a transmembrane domain, a co-stimulatory domain, and an intracellular T-cell signaling domain. In some cases, a recombinant protein provided herein (such as a CAR, e.g., on the surface of a cell) comprises, from the N-terminal end to the C-terminal end a V_H, a linker, a V_L, a transmembrane domain, a co-stimulatory domain, and an intracellular T-cell signaling domain. In some cases, a recombinant protein provided herein (such as a CAR, e.g., on the surface of a cell) comprises, from the N-terminal end to the C-terminal end a V_L, a linker, a V_H, a transmembrane domain, a co-stimulatory domain, and an intracellular T-cell signaling domain. In some cases, a recombinant protein provided herein (such as a CAR, e.g., on the surface of a cell) comprises, from the N-terminal end to the C-terminal end a V_H, a linker, a V_L, a hinge region, a transmembrane domain, a co-stimulatory domain, and an intracellular T-cell signaling domain. In some cases, a recombinant protein provided herein (such as a CAR, e.g., on the surface of a cell) comprises, from the N-terminal end to the C-terminal end a V_L, a linker, a V_H, a hinge region, a transmembrane domain, a co-stimulatory domain, and an intracellular T-cell signaling domain. The VH, VL, linker, hinge region, transmembrane domain, co-stimulatory domain, and intracellular T-cell signaling domain referred to in this paragraph, refer to those disclosed herein, including embodiments thereof.

[0189] In some cases, the T lymphocyte is a regulatory T lymphocyte (Treg). The category of effector T cell is a broad one that includes various T cell types that actively respond to a stimulus, such as co-stimulation. Effector T cells include helper, killer, regulatory, and potentially other T cell types. The regulatory T cells, formerly known as suppressor T cells, are a subpopulation of T cells which modulate the immune system, maintain tolerance to self-antigens, and prevent autoimmune disease. Tregs are immunosuppressive and generally suppress or downregulate induction and proliferation of effector T cells. In some cases, the effector T lymphocyte helper T cell. In some cases, the effector T lymphocyte is a killer T cell. In some cases, the effector T lymphocyte is a Treg.

[0190] In some cases, the Treg is a Treg that includes CD4positive-CD25high expression. In some cases, the Treg is a Treg that includes CD4positive-CD25high-CD127low or negative expression. In some cases, the Treg is a Treg that includes CD4positive-CD25high-CD6low or negative expression. In some cases, the Treg is a Treg that includes CD4positive-CD25high-CD127low or negative-CD6low or negative expression. In some cases, the Treg is a Treg that includes CD3positive-CD6low or negative expression. In some cases, the Treg is a Treg that includes CD4positive-CD6low or negative expression. In some cases, the Treg is a Treg that includes CD8positive-CD28low expression. In some cases, the Treg is a Treg that includes CD45RA+ expression. In some cases, the Treg is a Treg that does not include CD45RA+ expression. In some cases, the Treg is a Treg that includes FOXP3 demethylation. In some cases, the Treg is a Treg that does not include FOXP3 demethylation. In some cases, the Treg is a Treg that can be expanded either with IL-2 and/or rapamycin and/or retinoic acid. In some cases, the Treg is a Treg that can be expanded with IL-2 and/or rapamycin and/or retinoic acid. In some cases, the Treg is a Treg that can be expanded with IL-2. In some cases, the Treg is a Treg that can be expanded with rapamycin. In some cases, the Treg is a Treg that can be expanded with retinoic acid.

[0191] Determining "high" and "low" expression is well known in the art. A description of high and low expression of the markers referred to supra, and how high and low expression are determined and quantified, may be found, for example, in Putnam, A. L., T. M. Brusko, M. R. Lee, W. Liu, G. L. Szot, T. Ghosh, M. A. Atkinson and J. A. Bluestone. Expansion of human regulatory T-cells from patients with type 1 diabetes. Diabetes 58(3): 652-662, 2009; Bluestone J A, Buckner J H, Fitch M, Gitelman S E, Gupta S, Hellerstein M K, Herold K C, Lares A, Lee M R, Li K, Liu W, Long S A, Masiello L M, Nguyen V, Putnam A L, Rieck M, Sayre P H, Tang Q. Type 1 diabetes immunotherapy using polyclonal regulatory T cells. Sci Transl Med. 2015 Nov. 25; 7(315):315ra189; Fuchs, A., M. Gliwinski, N. Grageda, R. Spiering, A. K. Abbas, S. Appel, R. Bacchetta, M. Battaglia, D. Berglund, B. Blazar, J. A. Bluestone, M. Bornhauser, A. Ten Brinke, T. M. Brusko, N. Cools, M. C. Cuturi, E. Geissler, N. Giannoukakis, K. Golab, D. A. Hafler, S. M. van Ham, J. Hester, K. Hippen, M. Di Ianni, N. Ilic, J. Isaacs, F. Issa, D. Iwaszkiewicz-Grzes, E. Jaeckel, I. Joosten, D. Klatzmann, H. Koenen, C. van Kooten, O. Korsgren, K. Kretschmer, M. Levings, N. M. Marek-Trzonkowska, M. Martinez-Llordella, D. Miljkovic, K. H. G. Mills, J. P. Miranda, C. A. Piccirillo, A. L. Putnam, T. Ritter, M. G. Roncarolo, S. Sakaguchi, S. Sanchez-Ramon, B. Sawitzki, L. Sofronic-Milosavljevic, M. Sykes, Q. Tang, M. Vives-Pi, H. Waldmann, P. Witkowski, K. J. Wood, S. Gregori, C. M. U. Hilkens, G. Lombardi, P. Lord, E. M. Martinez-Caceres and P. Trzonkowski. Minimum Information about T Regulatory Cells: A Step toward Reproducibility and Standardization. Front Immunol 8: 1844, 2017; Duggleby, R., R. D. Danby, J. A. Madrigal and A. Saudemont. Clinical Grade Regulatory CD4(+) T Cells (Tregs): Moving Toward Cellular-Based Immunomodulatory Therapies. Front Immunol

9: 252, 2018; the entire contents of each of which are incorporated herein by reference in their entireties and for all purposes.

[0192] In some cases, an scFv (e.g., of a CAR) includes a light chain variable region set forth by SEQ ID NO:34. In some cases, the scFv includes a heavy chain variable region set forth by SEQ ID NO:35. In some cases, the scFv includes the sequence set forth by SEQ ID NO:38. In some cases, the scFv includes the sequence set forth by SEQ ID NO:39.

[0193] In some cases, an scFv (e.g., of a CAR) is oriented with a light chain variable region at the N-terminus followed by a heavy chain variable region. Alternatively, In some cases, the scFv is oriented with the heavy chain variable region at the N-terminus followed by the light chain variable region.

[0194] In some cases, the light chain variable region (VL) and the heavy chain variable region (VH) of the scFv are separated by a linker. In some cases, the linker comprises the sequence set forth by SEQ ID NO:36. In some cases, the linker comprises the sequence set forth by SEQ ID NO:37.

[0195] In some cases, the scFv amino acid sequence includes the sequence set forth by SEQ ID NO:38. In some cases, the scFv amino acid sequence includes the sequence set forth by SEQ ID NO:39. In some cases, the scFv amino acid sequence includes the sequence set forth by SEQ ID NO:40. In some cases, the scFv amino acid sequence includes the sequence set forth by SEQ ID NO:41.

[0196] In some cases, the light chain variable region is covalently bound to the transmembrane region through a hinge region. In some cases, the heavy chain variable region is covalently bound to the transmembrane region through a hinge region.

[0197] In some cases, the hinge region is a human IgG Fc. In some cases, the human IgG Fc is a human IgG4 Fc. In some cases, the human IgG Fc is a human IgG1 Fc.

[0198] In some cases, the co-stimulatory domain is a CD28 intracellular co-stimulatory domain or a variant thereof, a 4-1BB intracellular co-stimulatory domain or a variant thereof, an ICOS intracellular co-stimulatory signaling domain or a variant thereof, an OX-40 intracellular co-stimulatory signaling domain or a variant thereof, a CTLA-4 intracellular co-stimulatory signaling domain or a variant thereof, a PD-1 intracellular co-stimulatory signaling domain or a variant thereof, or a GITR intracellular co-stimulatory signaling domain or a variant thereof.

[0199] In some cases, the intracellular T-cell signaling domain is a CD3ζ intracellular T-cell signaling domain.

[0200] In some cases, the scFv comprises the CDR sequences set forth by SEQ ID NOs:28, 29, 30, 31, 32, and 33.

[0201] In an aspect is provided a T lymphocyte including any recombinant protein described herein including embodiments thereof. In some cases, the T lymphocyte is a regulatory T lymphocyte (Treg) as described herein, including embodiments thereof. CAR T cells may be produced using methods well known in the art. For example, T lymphocytes isolated from a subject (e.g. patient) or donor (e.g. healthy subject) may be transduced with a nucleic acid encoding a CAR or polypeptide described herein. Introduction of the nucleic acid encoding the CAR or polypeptide may be accomplished by viral or non-viral methods as described surpa. It should be appreciated that T lymphocytes obtained from donors (i.e. allogenic T lymphocytes) may undergo gene editing, using gene editing techniques well known in the art (e.g. CRISPR), to eliminate immunogenic proteins (e.g. native T cell receptors). Following transduction, the T lymphocytes may be activated using, for example, artificial antigen-presenting cells (APCs; e.g. engineered cell lines or antibody-coated magnetic beads). Once activated, the T lymphocytes may be induced to develop into specialized T cell subtypes (e.g. T regulatory cells) by treating with, for example, specific mixtures of cytokines. Finally, the CAR T cell population may be expanded using techniques well known in the art.

[0202] In some cases, the T lymphocyte including the recombinant protein described herein, including embodiments thereof, is an autologous T lymphocyte (i.e. taken from the subject). In some cases, the T lymphocyte including the recombinant protein described herein, including embodiments thereof, is an allogenic T lymphocyte (i.e. a T lymphocyte not obtained from the subject.) In some cases, the allogenic T lymphocyte has undergone gene editing. In some cases, the allogeneic T lymphocyte is gene edited to eliminate expression of a native T cell receptor protein.

[0203] In an aspect, an isolated nucleic acid encoding a protein (e.g. a CAR) including a single chain variable fragment (scFv) targeted to CD6 and a transmembrane domain is provided.

[0204] In an aspect, a vector including the nucleic acid (e.g., isolated nucleic acid) as provided herein including embodiments thereof is provided. In some cases, the vector is a composition of matter that comprises an isolated nucleic acid and that can be used to deliver the isolated nucleic acid to the interior of a cell. Numerous vectors are known in the art including, but not limited to, linear polynucleotides, polynucleotides associated with ionic or amphiphilic compounds, plasmids, and viruses. In some cases, the vector is an autonomously replicating plasmid or a virus. In some cases, a compound that facilitates transfer of nucleic acid into cells, such as, for example, a polylysine compound, liposome, and the like is used. Examples of viral transfer vectors include, but are not limited to, adenoviral vectors, adeno-associated virus vectors, retroviral vectors, lentiviral vectors, and the like. In some cases, the vector is a plasmid. In some cases, the vector is extrachromosomal. In some cases, the vector integrates into the genome of a cell. In some cases, the vector is a viral vector. In some cases, the virus is a lentivirus or onco-retrovirus. In some cases, the virus is a lentivirus. In some cases, the virus is an onco-retrovirus. Any suitable virus for delivery of a vector including the nucleic acid provided herein (e.g., the isolated nucleic acid) to a cell is contemplated In some cases, the vector comprises a recombinant polynucleotide comprising expression control sequences operatively linked to the nucleotide sequence to be expressed. The term "lentivirus" refers to a genus of the Retroviridae family. Lentiviruses are unique among the retroviruses in being able to infect non-dividing cells; they can deliver a significant amount of genetic information into the DNA of the host cell, so they are one of the most efficient methods of a gene delivery vector. HIV, SIV, and FIV are all examples of lentiviruses. The term "lentiviral vector" refers to a vector derived from at least a portion of a lentivirus genome, including especially a self-inactivating lentiviral vector as provided in Milone et al., Mol. Ther. 17(8): 1453-1464 (2009). Other examples of lentivirus vectors that may be used in the clinic, include but are not limited to, e.g., the LENTIVECTOR® gene delivery technology from Oxford BioMedica, the LENTIMAX™

vector system from Lentigen and the like. Nonclinical types of lentiviral vectors are also available and would be known to one skilled in the art.

[0205] In an aspect is provided a T lymphocyte including a vector provided herein, including embodiments thereof.

Methods of Treatment

[0206] In some embodiments, the compositions provided herein, including embodiments thereof, are used as effective treatment of autoimmune diseases. Thus, in an aspect is provided a method of treating an autoimmune disease (e.g., Type I diabetes, Graft-versus-Host Disease, Lupus), the method including administering to a subject in need thereof an effective amount of a T-lymphocyte (e.g., a CAR T-cell) provided herein including embodiments thereof.

[0207] In some cases, the autoimmune disease is associated with reduced islet cell (e.g., beta cell) function, viability, or survival. In some cases, the autoimmune disease is Type I Diabetes. In some cases, the autoimmune disease is Graft-versus-Host Disease. In some cases, the autoimmune disease includes a subject's immune system attacking the subject's islet cells (e.g., beta cells).

[0208] In some cases, the T-Lymphocyte provided herein, including embodiments thereof, suppresses CD6+ T-lymphocytes. In some cases, the T-Lymphocyte provided herein, including embodiments thereof, suppresses CD6+ B-lymphocytes.

[0209] In some embodiments, the compositions provided herein, including embodiments thereof, are used in a method of treating can tumor or cancer that expresses a CD6 and/or an CD19 and/or an IL-13 receptor (e.g., IL-13Rα2): including, e.g., glioblastoma, primary brain tumors and gliomas (glioblastoma multiforme WHO Grade IV, anaplastic astrocytoma WHO Grade III, low-grade astrocytoma WHO Grade II, pilocytic astrocytoma WHO Grade I, other ungraded gliomas, oligodendroglioma, gliosarcoma, ganglioglioma, meningioma, ependymona), neuroectodermal tumors (medulloblastoma, neuroblastoma, ganglioneuroma, melanoma (metastatic), melanoma (primary), pheochromocytoma, Ewing's sarcoma, primitive neuroectodermal tumors, small cell lung carcinoma, Schwannoma), other brain tumors (epidermoid cysts, brain tumors of unknown pathology, pituitary gland of glioblastoma multiforme pt., metastatic tumors to brain of unknown tissue origin), melanoma, melanoma metastases, breast cancer, breast cancer metastases, kidney cancer, kidney cancer metastases, liver cancer, liver cancer metastases, lung cancer, lung cancer metastases, lymphoma, lymphoma metastases, ovarian cancer, ovarian cancer metastases, pancreatic cancer, pancreatic cancer metastases, prostate cancer, prostate cancer metastases, colorectal cancer, colorectal cancer metastases, combinations thereof, and the like, in a patient comprising administering a population of autologous or allogeneic human T cells transduced by a vector comprising a nucleic acid molecule described herein. In various embodiments: a chimeric antigen receptor described herein is administered locally or systemically; in some embodiments, a method of treatment includes reducing or eliminating cells expressing one or more of a CD6 receptor and/or an CD19 receptor and/or IL-13Rα2, and the cells are cancerous cells; and a chimeric antigen receptor or polypeptide described herein or a T cell expressing a CAR or polypeptide (e.g., CAR Teff or CAR Treg) described herein is administered by single or repeat dosing.

EXAMPLES

[0210] The following examples are intended to further illustrate certain embodiments of the disclosure. The examples are put forth so as to provide one of ordinary skill in the art and are not intended to limit its scope.

Example 1: CD6-Targeted, CD19-Targeted, and IL-13 CAR Expressed in Treg

[0211] Various CAR that include an scFv derived from Itolizumab are depicted in FIG. **1** to FIG. **4**. Each includes, in addition to an scFv in either the VL or VH orientation: a spacer derived from a portion of IgG4 with certain mutations, a CD4 transmembrane domain, either a CTLA4 or 4-1BB signaling domain, and a CD3 zeta signaling domain. CAR were prepared with the scFv in VH-VL or VL-VH orientations because yeast surface display technology previously suggested that a VH-VL scFv has an affinity for human CD6 that is similar to Itolizumab while a VL-VH scFv has lower affinity for human CD6 (Garner et al. (2018) *Immunology* 155:273). FIG. **8** is schematic depiction of a method used to isolate Tregs and Tregs that are $CD6^{low/-}$. Tregs can be isolated using any appropriate method (Fuchs et al. (2018) Front Immunol. 8:1844; Duggleby et al. (2018) *Front Immunol.* 9:252). CAR expressing IL-13 or an scFv targeting CD19, in either the VL or VH orientation, were also made using similar methods. Each includes a spacer derived from a portion of IgG4 with certain mutations, a CD4 transmembrane domain, either a CTLA4 or a 4-1BB signaling domain, and a CD3 zeta signaling domain. FIG. **5** depicts the amino acid sequence of an alternative CD6 scFv that can replace the scFv in any of the constructs depicted in FIGS. **1-4**.

[0212] A comparison of Treg, Treg expressing a CD6 CAR (CTLA4), and a CD6 CAR (4-1BB) shows that the CD6 CAR with CTLA4 signaling domain is superior for reducing Teff (CD4+) proliferation (FIG. **6**). In addition, the CD6 CAR with CTLA4 signaling domain is superior for reducing target Teff proliferation (FIG. **7**). The Treg expressing CD6 elicited anti-inflammatory cytokines (FIG. **8**). As shown in FIG. **10**, Tregs expressing a CD6 CAR with a CTLA4 signaling domain can be cultured in the presence of Teff while expressing relatively low levels of exhaustion markers.

Example 2: Expression and Characterization of CD6-Targeted CAR

[0213] The CD6-targeted CAR can be expressed in Tregs using a lentiviral vector, amongst other methods. A suitable lentiviral vector is described in WO 2016/044811. The nucleotide sequence expressing the CAR can be in frame with a sequence encoding T2A (LEGGGEGRGSLLTCGDVEENPGPR; SEQ ID NO:71) and a sequence encoding a truncated CD19 receptor (MPPPRLLFFLLFLTPMEVRPEEPLVVKVEEGD-
NAVLQCLKGTSDGPTQQLTWSRESPLK
PFLKLSLGLPGLGIHMRPLAIWLFIFNVSQQMGGFYL-
CQPGPPSEKAWQPGWTVNVEGS GELFRWNVSDLG-
GLGCGLKNRSSEGPSSPSGKLMSPKLYVWAKDRPEI-
WEGEPPCVPPR
DSLNQSLSQDLTMAPGSTLWLSCGVPPDSVSRG-
PLSWTHVHPKGPKSLLSLELKDDRPA
RDMWVMETGLLLPRATAQDAGKYY-
CHRGNLTMSFHLEITARPVLWHWLLRTGGWKV

SAVTLAYLIFCLCSLVGILHLQRALVLRRKR; SEQ ID NO:73). When expressed in this manner, the CAR is coordinately expressed with a truncated CD19. This facilitates quantification and purification via tagged pull-down of CAR-expressing cells using readily available CD19 antibodies.

[0214] FIG. **7** depicts a binding assay that determined the dissociation constant (K_D) of a representative CD6 CAR Treg compared to a high affinity CD6 CAR Treg and a low affinity CD6 CAR Treg. The K_D for the CD6 CAR Tregs were 50.0±2.9 nM, 7.9±2.0 nM, and 129.5±12.1 nM for the CD6 CAR Treg, high affinity CD6 CAR Treg, and low affinity CD6 CAR Treg. Three substitutions between the CD6 CAR Treg and the high affinity CD6 CAR Treg are R to G at H_{44} FR2, S to G at $Linker_{18}$ and L to M at L_{104}FR4. Without being bound by theory, using a CAR that is neither high affinity nor low affinity may have similar therapeutic effect and reduced side effects. Thus, a CAR described herein can specifically target and kill cancers cells while reducing overall side effects.

[0215] FIG. **9** depicts transduction of the anti-CD6 CAR into Tregs. Blue are the CD6 CAR using an antibody against the CD19 tag and pink are Tregs. Both the CD6 CAR with the 41BB signaling domain and the CD6 CAR with the CTLA4 signaling domain showed good transduction at both day 9 and day 14. FIG. **10** depicts FACS analysis of CD4 and CD8 presence on the CD6 CAR Tregs compared to mock transduced. Mock Tregs were 97.4% CD4+, CD8− and 1.64% CD4+, CD8+. The CD6 CAR Treg with the 41BB signaling domain were 98.0% CD4+, CD8− and 1.10% CD4+, CD8+. The CD6 CAR Treg with the CTLA4 signaling domain were 97.5% CD4+, CD8− and 1.32% CD4+, CD8+. Thus, a CAR Treg described herein can retain the CD4+ phenotype up to 14 days post-induction. FIG. **11** depicts cell expansion of the CD6 CAR Tregs compared to mock and Teff Cell expansion was induced by the addition of 500 IU/mL IL-2 for Tregs and 50 IU/mL IL-2 plus 0.15 mg/mL IL-15 for Teff. This showed that the CD6 CAR with the 41BB signaling domain and the CD6 CAR with the CTLA4 signaling domain showed good expansion up through day 14 in all patient samples. FIG. **12** depicts Mean Fluoro Intensity (MFI) of either CD6 or CTLA4 surface expression on cells. PMBC and Teff showed high CD6 at the cell surface, and Tregs showed low CD6 cell surface expression, as expected. Both the CD6 CAR Treg with the 41BB signaling domain and the CD6 CAR Treg with the CTLA4 signaling domain showed low CD6 expression at the cell surface, similar to that of regular Treg. Without being bound by theory, this reduces self-targeting of CD6 CAR Tregs. PMBC and Teff showed low CTLA4 at the cell surface, and Tregs showed high CTLA4 cell surface expression, as expected. Both the CD6 CAR Treg with the 41BB signaling domain and the CD6 CAR Treg with the CTLA4 signaling domain showed high CTLA4 expression at the cell surface, similar to that of regular Treg. Without being bound by theory, this maintains signaling pathways of CD6 CAR Tregs. Thus, expression of a CAR described herein does not alter the Treg phenotype at the cell surface. FIG. **13** depicts a FOXP3 Treg-specific demythylated region (TSDR) methylation assay. PMBC and Teff cells had low unmethylated FOXP3 levels. Treg had high level of unmethylated FOXP3 as expected. Mock Treg had high level of unmethylated FOXP3. Both the CD6 CAR Treg with the 41BB signaling domain and the CD6 CAR Treg with the CTLA4 signaling domain showed high unmethylated FOXP3, similar to that of regular Treg. It should be noted that in some instances, results in a FOXP3 TSDR methylation assay are multiplied by 2; however, that was not done in FIG. **13**. Taken together, the results showed that expression of the CD6 CAR with the 41BB signaling domain or with the CTLA4 signaling domain does not alter the Treg phenotype. Thus, CAR Tregs described herein have good purity, transduction, expansion, and Treg phenotype (CD4+, CD6−, CTLA4+, and unmethylated FOXP3) with low exhaustion.

Example 3: Antigen-Specific Proliferation and Targeted Killing of Cancer Cells by CAR Tregs

[0216] FIG. **14**A depicts a schematic of the experimental design used to detect antigen-specific stimulation of tag-purified CD6 CAR Tregs with either a 41BB signaling domain or a CTLA4 signaling domain. The CD6 CAR Tregs were exposed to CD6 as they would be exposed to in a tumor microenvironment. FIG. **14**B shows that both the CD6 CAR Tregs with a 41BB signaling domain and the CD6 CAR Tregs with a CTLA4 signaling domain showed strong proliferation, even in the absence of IL-2. Both the CD6 CAR Tregs with a 41BB signaling domain and the CD6 CAR Tregs with a CTLA4 signaling domain also showed strong cytokine expression profiles. CD6 CAR Tregs with a 41BB signaling domain showed high levels of both pro-inflammatory and anti-inflammatory cytokines, with particularly high levels of IL-5 and IL-13. CD6 CAR Tregs with a CTLA4 signaling domain showed high levels of primarily anti-inflammatory cytokines, with high levels of IL-5, IL-10, and IL-13. Without being bound by theory, the CAR Tregs described herein can be used to target a cancer and/or auto-immune disease.

[0217] FIG. **15**A depicts a schematic of the experimental design used to detect antigen-specific killing of a CD6+ human cancer cell by CD6 CAR Tregs with either a 41BB signaling domain or a CTLA4 signaling domain. The HuT78 cell line is derived from human cutaneous T lymphocytes from a 53 year old male Sezary Syndrome patient. FIG. **15**B shows the HuT78 cell line had high CD6 expression. FIG. **15**C depicts CAR Treg-induced cell death. Briefly, HuT78 cells (100,000) were co-incubated in vitro for 96 hours with Tregs transduced with an anti-CD6 CAR at 1:1 ratio. Cell survival in the treatment groups was then compared to the tumor cells alone. Both the CD6 CAR Tregs with a 41BB signaling domain and the CD6 CAR Tregs with a CTLA4 signaling domain showed killing of the CD6-positive HuT78 cells. Thus, CAR Tregs described herein have strong antigen-specific proliferation and killing of the targeted cancer cells.

Example 4: Cytokine Release and Target Cell Killing Efficacy of CAR Tregs and CAR Teffs

[0218] FIG. **22**A shows a schematic depiction of a Treg expressing either CD6scFvop(VH-VL) CAR with a 41BB domain or CD6scFvop(VH-VL) CAR with a CTLA domain that can bind to a Teff expressing CD6 on its cell surface. The two CD6 CAR Tregs were compared to mock Tregs. FIG. **22**B shows cytokine concentration of TNF, IFNγ, GM-CSF, and IL-10 produced by Treg (first column on left; mock), Treg CAR^{41BB} (middle column), and Treg CAR^{CTLA} (third column). Briefly, the Tregs were exposed to plate-bound anti-CD6-Fc for 4 days, after which the cytokines

levels were measured. Generally, the CD6 CAR^{41BB} had less cytokines released compared to the CD6 CAR^{CTLA} in this assay. FIG. **22**C shows the change in cytokine levels in percent (proinflammatory cytokines, cytokine release syndrome (CRS) cytokines, and anti-inflammatory cytokines) of Tregs versus Teff. The far left (first) column for each cytokine measured is Treg (mock), the middle column is Treg CAR^{41BB}, and the third column is Treg CAR^{CTLA}. Briefly, T effector cells (Teff) purified from healthy human donors and stimulated with plate-bound CD3 mAb were co-cultured for four days at a 1:1 ratio with autologous regulatory T cells (Treg) or transduced Treg with the anti-CD6 CAR with the 41BB or CTLA4 signaling domain. Cytokines were assessed in supernatants using Luminex Performance Human XL16 plex kit (R&D) on the FLEXMAP 3D System. Generally, the CD6 CAR^{CTLA} had less net cytokine levels in proinflammatory and CRS cytokines compared to the CD6 CAR^{41BB} in this assay. The CD6 CAR^{41BB} had more net cytokine levels in anti-inflammatory and CRS cytokines compared to the CD6 CAR^{41BB} in this assay. FIG. **22**D shows antigen-specific tumor cell death of $CD6^+$ Teff cells by the Tregs. Briefly, tumor $CD6^+$ cells were co-cultured with Tregs (mock, CD6 CAR^{41BB}, and CD6 CAR^{CTLA}) at a 1:1 ratio for four days. Reduced tumor cell count shows CD6-specific tumor killing by the Tregs. FIG. **22**E shows the percent of CAR Treg (CD6 CAR^{41BB} and CD6 CAR^{CTLA}) needed to achieve the IC50 of Tregs (no CAR). IC50 here is the amount of Tregs required to suppress Teff proliferation by 50%. Generally, it would take less CD6 CAR^{CTLA} and about the same or less CD6 CAR^{41BB} to achieve the same IC50 as Treg.

[0219] FIG. **23**A shows a schematic depiction of a Teff expressing either an IL-13 CAR with a 41BB domain or an IL-13 CAR with a CTLA domain that can bind to a tumor cell expressing IL13αR2 on its surface. FIG. **23**B shows cellular expansion of Teffs (mock, IL13 CAR^{41BB}, or IL13 CAR^{CTLA4}) up to 14 days post-induction. The Teffs showed about equal expansion. FIG. **23**C shows cytokine release (concentration of TNF (pro-inflammatory), IFNγ (pro-inflammatory), GM-CSF (CRS), IL-10 (anti-inflammatory) measured) of Teffs. Briefly, Teff (mock), Teff IL13 CAR^{41BB}, and Teff IL13 CAR^{CTLA} were each co-cultured for 24 hours with HT1080 tumor cells that express IL13αR2 on its surface, after which cytokines levels were measured. Generally, the IL13 CAR^{CTLA} had less cytokines released compared to the CD6 CAR^{41BB} in this assay. FIG. **23**D shows antigen-specific cell lysis of tumor cells by Teff (mock), Teff IL13 CAR^{41BB}, and Teff IL13 CAR^{CTLA}. Briefly, Teff (mock), Teff IL13 CAR^{41BB}, and Teff IL13 CAR^{CTLA} were each co-cultured for 24 hours with HT1080 tumor cells that express IL13αR2 on its surface at three different tumor:Teff cell ratios (1:1, 1:0.5, and 1:0.25). Increased cell lysis shows antigen-specific tumor killing by the Teffs. Both Teff IL13 CAR^{41BB} and Teff IL13 CAR^{CTLA} resulted in comparable specific lysis of tumor cells.

[0220] FIG. **24** shows a schematic depiction of the interaction between a CAR T cell of the disclosure, the mechanism of action, and enumerated advantages of each step. Advantages include (1) CAR transduced T cells produced a tuned activation signaling upon antigen-specific recognition; (2) Blunted cytokine release; (3) Less off-target effects (reducing CRS); (4) Minimized local and systemic tissue damage; (5) CAR T-cell life span extension; and (6) Equal or increased anti-cancer efficacy.

OTHER EMBODIMENTS

[0221] It is to be understood that while the invention has been described in conjunction with the detailed description thereof, the foregoing description is intended to illustrate and not limit the scope of the invention, which is defined by the scope of the appended claims. Other aspects, advantages, and modifications are within the scope of the following claims.

INFORMAL PARTIAL SEQUENCE LISTING

SEQ ID NO: 1

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RLEASWEPACGALWDSRAAEAVCRALGCGGAEAASQLAPPTPELPPPPAAGNTSVAAN

ATLAGAPALLCSGAEWRLCEVVEHACRSDGRRARVTCAENRALRLVDGGGACAGRVE

MLEHGEWGSVCDDTWDLEDAHVVCRQLGCGWAVQALPGLHFTPGRGPIHRDQVNCS

GAEAYLWDCPGLPGQHYCGHKEDAGAVCSEHQSWRLTGGADRCEGQVEVHFRGVWN

TVCDSEWYPSEAKVLCQSLGCGTAVERPKGLPHSLSGRMYYSCNGEELTLSNCSWRFN

NSNLCSQSLAARVLCSASRSLHNLSTPEVPASVQTVTIESSVTVKIENKESRELMLLIPSIV

LGILLLGSLIFIAFILLRIKGKYALPVMVNHQHLPTTIPAGSNSYQPVPITIPKEVFMLPIQV

QAPPPEDSDSGSDSDYEHYDFSAQPPVALTTFYNSQRHRVTDEEVQQSRFQMPPLEEGL

EELHASHIPTANPGHCITDPPSLGPQYHPRSNSESSTSSGEDYCNSPKSKLPPWNPQVFSS

ERSSFLEQPPNLELAGTQPAFSAGPPADDSSSTSSGEWYQNFQPPPQPPSEEQFGCPGSPS

PQPDSTDNDDYDDISAA

SEQ ID NO: 2

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TLAGAPALLCSGAEWRLCEVVEHACRSDGRRARVTCAENRALRLVDGGGACAGRVEM

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EAYLWDCPGLPGQHYCGHKEDAGAVCSEHQSWRLTGGADRCEGQVEVHFRGVWNTV

CDSEWYPSEAKVLCQSLGCGTAVERPKGLPHSLSGRMYYSCNGEELTLSNCSWRFNNS

NLCSQSLAARVLCSASRSLHNLSTPEVPASVQTVTIESSVTVKIENKESRELMLLIPSIVLG

ILLLGSLIFIAFILLRIKGKYVFMLPIQVQAPPPEDSDSGSDSDYEHYDFSAQPPVALTTFY

NSQRHRVTDEEVQQSRFQMPPLEEGLEELHASHIPTANPGHCITDPPSLGPQYHPRSNSES

STSSGEDYCNSPKSKLPPWNPQVFSSER

SSFLEQPPNLELAGTQPAFSGSPSPQPDSTDNDDYDDISAA

SEQ ID NO: 3

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ATLAGAPALLCSGAEWRLCEVVEHACRSDGRRARVTCAENRALRLVDGGGACAGRVE

MLEHGEWGSVCDDTWDLEDAHVVCRQLGCGWAVQALPGLHFTPGRGPIHRDQVNCS

GAEAYLWDCPGLPGQHYCGHKEDAGAVCSEHQSWRLTGGADRCEGQVEVHFRGVWN

TVCDSEWYPSEAKVLCQSLGCGTAVERPKGLPHSLSGRMYYSCNGEELTLSNCSWRFN

NSNLCSQSLAARVLCSASRSLHNLSTPEVPASVQTVTIESSVTVKIENKESRELMLLIPSIV

LGILLLGSLIFIAFILLRIKGKYALPVMVNHQHLPTTIPAGSNSYQPVPITIPKEDSQRHRVT

DEEVQQSRFQMPPLEEGLEELHASHIPTANPGHCITDPPSLGPQYHPRSNSESSTSSGEDY

CNSPKSKLPPWNPQVFSSERSSFLEQPPNLELAGTQPAFSGSPSPQPDSTDNDDYDDISAA

SEQ ID NO: 4

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SEQ ID NO: 5

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YPPPYLDNEKSNGTIIHVKGKHLCPSPLFPGPSKPFWVLVVVGGVLACYSLLVTVAFIIF

WVRSKRSRLLHSDYMNMTPRRPGPTRKHYQPYAPPRDFAAYRS

SEQ ID NO: 7

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SEQ ID NO: 8

RSKRSRLLHSDYMNMTPRRPGPTRKHYQPYAPPRDFAAYRS

SEQ ID NO: 9

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QIKILGNQGSFLTKGPSKLNDRADSRRSLWDQGNFPLIIKNLKIEDSDTYICEVEDQKEEV

QLLVFGLTANSDTHLLQGQSLTLTLESPPGSSPSVQCRSPRGKNIQGGKTLSVSQLELQD

SGTWTCTVLQNQKKVEFKIDIVVLAFQKASSIVYKKEGEQVEFSFPLAFTVEKLTGSGEL

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WWQAERASSSKSWITFDLKNKEVSVKRVTQDPKLQMGKKLPLHLTLPQALPQYAGSG

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KREKAVWVLNPEAGMWQCLLSDSGQVLLESNIKVLPTWSTPVQPMALIVLGGVAGLLL

FIGLGIFFCVRCRHRRRQAERMSQIKRLLSEKKTCQCPHRFQKTCSPI

SEQ ID NO: 10

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QAERASSSKSWITFDLKNKEVSVKRVTQDPKLQMGKKLPLHLTLPQALPQYAGSGNLT

LALEAKTGKLHQEVNLVVMRATQLQKNLTCEVWGPTSPKLMLSLKLENKEAKVSKRE

KAVWVLNPEAGMWQCLLSDSGQVLLESNIKVLPTWSTPVQPMALIVLGGVAGLLLFIG

LGIFFCVRCRHRRRQAERMSQIKRLLSEKKTCQCPHRFQKTCSPI

SEQ ID NO: 11

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WGPTSPKLMLSLKLENKEAKVSKREKAVWVLNPEAGMWQCLLSDSGQVLLESNIKVLP

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HRFQKTCSPI

SEQ ID NO: 12

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HRFQKTCSPI

SEQ ID NO: 13

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HRFQKTCSPI

SEQ ID NO: 14

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SEQ ID NO: 15

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TCDICRQCKGVFRTRKECSSTSNAECDCTPGFHCLGAGCSMCEQDCKQGQELTKKGCK

DCCFGTFNDQKRGICRPWTNCSLDGKSVLVNGTKERDVVCGPSPADLSPGASSVTPPAP

AREPGHSPQIISFFLALTSTALLFLLFFLTLRFSVVKRGRKKLLYIFKQPFMRPVQTTQEED

GCSCRFPEEEEGGCEL

SEQ ID NO: 16

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SEQ ID NO: 17

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(VL NA)

SEQ ID NO: 18

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CATTCACATTCGGAAGTGGTACGAAACTCGAGATCAAACGGGCA

(VH NA)

SEQ ID NO: 19

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TATATATTATCCCGACTCCGTCAAAGGAAGGTTCACGATTTCAAGGGACAATGTGAA

GAACACCCTCTACTTACAGATGAGTAGTCTGCGTTCTGAGGATACCGCTATGTACTA

CTGTGCTCGGAGAGATTACGATCTGGATTATTTCGACAGCTGGGGTCAGGGCACACT

CGTTACAGTATCCTCG

(VH CDR1 NA)

SEQ ID NO: 20

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AAGT

(VH CDR2 NA)

SEQ ID NO: 21

TTCTCTCGGTACGCTATGTCGTGGGTCAGACAAGCGCCCGGCAAA

(VH CDR3 NA)

SEQ ID NO: 22

CGTGATTATGATCTAGACTACTTTGACTCCTGGGGTCAAGGTACGCTCGTGACGGTT

SEQ ID NO: 23

MALIVLGGVAGLLLFIGLGIFF

SEQ ID NO: 24

ATGGCCCTGATTGTGCTGGGGGGCGTCGCCGGCCTCCTGCTTTTCATTGGGCTAGGC

ATCTTCTTC

SEQ ID NO: 25

IYIWAPLAGTCGVLLLSLVIT

(Linker 18 NA)

SEQ ID NO: 26

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(Linker 20 NA)

SEQ ID NO: 27

GGCGGCGGCGGAAGTGGCGGCGGCGGCTCAGGCGGGGGGGGTTCTGGGGGCGGCG

GTTCA

(VH CDR1 AA)

SEQ ID NO: 28

VQLVESGGGLVKPGGSLKLS

(VH CDR2 AA)

SEQ ID NO: 29

FSRYAMSWVRQAPGK

(VH CDR3 AA)

SEQ ID NO: 30

RDYDLDYFDSWGQGTLVTV

(VL CDR1 AA)

SEQ ID NO: 31

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SEQ ID NO: 32

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SEQ ID NO: 33

CSRAARGTIGARRTGQPLKEDPSAVPVFSVDYGELDFQWREKTPEPPVPCVPEQTEYATI

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(VL AA)

SEQ ID NO: 34

DIQMTQSPSSLSASVGDRVTITCKASRDIRSYLTWYQQKPGKAPKTLIYYATSLADGVPS

RFSGSGSGQDYSLTISSLESDDTATYYCLQHGESPFTFGSGTKLEIKRA

(VH AA)

SEQ ID NO: 35

EVQLVESGGGLVKPGGSLKLSCAASGFKFSRYAMSWVRQAPGKRLEWVATISSGGSYI

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TVSS

(Linker 18 AA)

SEQ ID NO: 36

GSTSGGGSGGGSGGGGSS

(Linker 20 AA)

SEQ ID NO: 37

GGGGSGGGGSGGGGSGGGGS

(Full scFv (VH-VL) linker 18)

SEQ ID NO: 38

EVQLVESGGGLVKPGGSLKLSCAASGFKFSRYAMSWVRQAPGKRLEWVATISSGGSYI

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TVSS

GSTSGGGSGGGSGGGGSSDIQMTQSPSSLSASVGDRVTITCKASRDIRSYLTWYQQKPG

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KLEIKRA

(Full scFv (VH-VL) linker 20)

SEQ ID NO: 39

EVQLVESGGGLVKPGGSLKLSCAASGFKFSRYAMSWVRQAPGKRLEWVATISSGGSYI

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TVSS

GGGGSGGGGSGGGGSGGGGSDIQMTQSPSSLSASVGDRVTITCKASRDIRSYLTWYQQK

PGKAPKTLIYYATSLADGVPSRFSGSGSGQDYSLTISSLESDDTATYYCLQHGESPFTFGS

GTKLEIKRA

(Full scFv (VL-VH) linker 18 AA)

SEQ ID NO: 40

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(Full scFv (VL-VH) linker 20 AA)

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SWGQGTLVTVSS

(Full scFv (VH-VL) linker 18 NA)

SEQ ID NO: 42

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GAACACCCTCTACTTACAGATGAGTAGTCTGCGTTCTGAGGATACCGCTATGTACTA

CTGTGCTCGGAGAGATTACGATCTGGATTATTTCGACAGCTGGGGTCAGGGCACACT

CGTTACAGTATCCTCGGGGTCAACGTCGGGCGGGGGTTCCGGTGGAGGAAGTGGAG

GTGGTGGAAGTTCTGACATCCAAATGACACAAAGTCCTAGCTCTCTCTCAGCAAGTG

TTGGCGACCGTGTGACCATCACATGTAAAGCTTCAAGGGATATTCGCAGCTACCTGA

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CACGGGGAAAGCCCATTCACATTCGGAAGTGGTACGAAACTCGAGATCAAACGGGC

A

(Full scFv (VH-VL) linker 20 NA)

SEQ ID NO: 43

GAAGTCCAATTGGTCGAGAGCGGAGGTGGGCTTGTTAAACCAGGAGGCAGTTTAAA

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GAACACCCTCTACTTACAGATGAGTAGTCTGCGTTCTGAGGATACCGCTATGTACTA

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CGTTACAGTATCCTCGGGCGGCGGCGGAAGTGGCGGCGGCGGCTCAGGCGGGGGGG

GTTCTGGGGGCGGCGGTTCAGACATCCAAATGACACAAAGTCCTAGCTCTCTCTCAG

CAAGTGTTGGCGACCGTGTGACCATCACATGTAAAGCTTCAAGGGATATTCGCAGCT

ACCTGACTTGGTACCAACAAAAGCCCGGAAAAGCGCCTAAAACGCTTATTTACTAT

GCCACCAGCCTCGCAGATGGTGTCCCCTCCAGATTTTCTGGATCGGGATCAGGGCAA

GATTATAGTCTTACGATATCGAGTCTTGAGTCGGACGATACTGCCACATACTACTGC

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ACGGGCA

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(Full scFv (VL-VH) linker 18 NA)

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CATTCACATTCGGAAGTGGTACGAAACTCGAGATCAAACGGGCAGGGTCAACGTCG

GGCGGGGGTTCCGGTGGAGGAAGTGGAGGTGGTGGAAGTTCTGAAGTCCAATTGGT

CGAGAGCGGAGGTGGGCTTGTTAAACCAGGAGGCAGTTTAAAATTATCATGTGCTG

CCTCGGGTTTCAAGTTCTCGCGGTATGCTATGTCCTGGGTACGCCAAGCACCTGGAA

AGCGTTTAGAATGGGTGGCCACAATTAGTAGTGGTGGTTCATATATATATTATCCCG

ACTCCGTCAAAGGAAGGTTCACGATTTCAAGGGACAATGTGAAGAACACCCTCTAC

TTACAGATGAGTAGTCTGCGTTCTGAGGATACCGCTATGTACTACTGTGCTCGGAGA

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TCG

(Full scFv (VL-VH) linker 20 NA)

SEQ ID NO: 45

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TGTCCCCTCCAGATTTTCTGGATCGGGATCAGGGCAAGATTATAGTCTTACGATATC

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CATTCACATTCGGAAGTGGTACGAAACTCGAGATCAAACGGGCAGGCGGCGGCGGA

AGTGGCGGCGGCGGCTCAGGCGGGGGGGGTTCTGGGGGCGGCGGTTCAGAAGTCCA

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GTGCTGCCTCGGGTTTCAAGTTCTCGCGGTATGCTATGTCCTGGGTACGCCAAGCAC

CTGGAAAGCGTTTAGAATGGGTGGCCACAATTAGTAGTGGTGGTTCATATATATATT

ATCCCGACTCCGTCAAAGGAAGGTTCACGATTTCAAGGGACAATGTGAAGAACACC

CTCTACTTACAGATGAGTAGTCTGCGTTCTGAGGATACCGCTATGTACTACTGTGCT

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GTATCCTCG

SEQ ID NO: 46

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ACDIYIWAPLAGTCGVLLLSLVITLYCNHRNRRRVCKCPRPVVKSGDKPSLSARYV

SEQ ID NO: 47

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CPRPVVKSGDKPSLSARYV

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SEQ ID NO: 48

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PRGAAASPTFLLYLSQNKPKAAEGLDTQRFSGKRLGDTFVLTLSDFRRENEGYYFCSAL

SNSIMYFSHFVPVFLPAKPTTTPAPRPPTPAPTIASQPLSLRPEACRPAAGGAVHTRGLDF

ACDIYIWAPLAGTCGVLLLSLVITLYCNHRNRRRVCKCPRPVVKSGDKPSLSARYV

SEQ ID NO: 49

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QAPSSDSHHEFLALWDSAKGTIHGEEVEQEKIAVFRDASRFILNLTSVKPEDSGIYFCMIV

GSPELTFGKGTQLSVVDFLPTTAQPTKKSTLKKRVCRLPRPETQKGPLCSPITLGLLVAG

VLVLLVSLGVAIHLCCRRRRARLRFMKQKFNIVCLKISGFTTCCCFQILQMSREYGFGVL

LQKDIGQ

SEQ ID NO: 50

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QAPSSDSHHEFLALWDSAKGTIHGEEVEQEKIAVFRDASRFILNLTSVKPEDSGIYFCMIV

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ACMDTTAILQPHRSCLTHGS

SEQ ID NO: 51

MRPRLWLLLAAQLTVLHGNSVLQQTPAYIKVQTNKMVMLSCEAKISLSNMRIYWLRQR

QAPSSDSHHEFLALWDSAKGTIHGEEVEQEKIAVFRDASRFILNLTSVKPEDSGIYFCMIV

GSPELTFGKGTQLSVVDFLPTTAQPTKKSTLKKRVCRLPRPETQKGPLCSPITLGLLVAG

VLVLLVSLGVAIHLCCRRRRARLRFMKQPQGEGISGTPVPQCLHGYYSNTTTSQKLLNP

WILKT

SEQ ID NO: 52

MRPRLWLLLAAQLTVLHGNSVLQQTPAYIKVQTNKMVMLSCEAKISLSNMRIYWLRQR

QAPSSDSHHEFLALWDSAKGTIHGEEVEQEKIAVFRDASRFILNLTSVKPEDSGIYFCMIV

GSPELTFGKGTQLSVVDFLPTTAQPTKKSTLKKRVCRLPRPETQKGRRRRARLRFMKQP

QGEGISGTFVPQCLHGYYSNTTTSQKLLNPWILKT

SEQ ID NO: 53

MRPRLWLLLAAQLTVLHGNSVLQQTPAYIKVQTNKMVMLSCEAKISLSNMRIYWLRQR

QAPSSDSHHEFLALWDSAKGTIHGEEVEQEKIAVFRDASRFILNLTSVKPEDSGIYFCMIV

GSPELTFGKGTQLSVVDFLPTTAQPTKKSTLKKRVCRLPRPETQKGPLCSPITLGLLVAG

VLVLLVSLGVAIHLCCRRRRARLRFMKQLRLHPLEKCSRMDY

SEQ ID NO: 54

MRPRLWLLLAAQLTVLHGNSVLQQTPAYIKVQTNKMVMLSCEAKISLSNMRIYWLRQR

QAPSSDSHHEFLALWDSAKGTIHGEEVEQEKIAVFRDASRFILNLTSVKPEDSGIYFCMIV

GSPELTFGKGTQLSVVDFLPTTAQPTKKSTLKKRVCRLPRPETQKGPLCSPITLGLLVAG

VLVLLVSLGVAIHLCCRRRRARLRFMKQFYK

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SEQ ID NO: 55

MKWKALFTAAILQAQLPITEAQSFGLLDPKLCYLLDGILFIYGVILTALFLRVKFSRSADA

PAYQQGQNQLYNELNLGRREEYDVLDKRRGRDPEMGGKPRRKNPQEGLYNELQKDK

MAEAYSEIGMKGERRRGKGHDGLYQGLSTATKDTYDALHMQALPPR

SEQ ID NO: 56

MKWKALFTAAILQAQLPITEAQSFGLLDPKLCYLLDGILFIYGVILTALFLRVKFSRSADA

PAYQQGQNQLYNELNLGRREEYDVLDKRRGRDPEMGGKPQRRKNPQEGLYNELQKDK

MAEAYSEIGMKGERRRGKGHDGLYQGLSTATKDTYDALHMQALPPR

SEQ ID NO: 57

MLRLLLALNLFPSIQVTGNKILVKQSPMLVAYDNAVNLSWKHLCPSPLFPGPSKPFWVL

VVVGGVLACYSLLVTVAFIIFWVRSKRSRLLHSDYMNMTPRRPGPTRKHYQPYAPPRDF

AAYRS

SEQ ID NO: 58

MLRLLLALNLFPSIQVTGKHLCPSPLFPGPSKPFWVLVVVGGVLACYSLLVTVAFIIFWV

RSKRSRLLHSDYMNMTPRRPGPTRKHYQPYAPPRDFAAYRS

SEQ ID NO: 59

MLRLLLALNLFPSIQVTGNKILVKQSPMLVAYDNAVNLSCKYSYNLFSREFRASLHKGL

DSAVEVCVVYGNYSQQLQVYSKTGFNCDGKLGNESVTFYLQNLYVNQTDIYFCKIEVM

YPPPYLDNEKSNGTIIHVKGKHLCPSPLFPGPSKPFWVLVVVGGVLACYSLLVTVAFIIF

WVRSKRSRLLHSDYMNMTPRRPGPTRKHYQPYAPPRDFAAYRS

SEQ ID NO: 60

MCVGARRLGRGPCAALLLLGLGLSTVTGLHCVGDTYPSNDRCCHECRPGNGMVSRCSR

SQNTVCRPCGPGFYNDVVSSKPCKPCTWCNLRSGSERKQLCTATQDTVCRCRAGTQPL

DSYKPGVDCAPCPPGHFSPGDNQACKPWTNCTLAGKHTLQPASNSSDAICEDRDPPATQ

PQETQGPPARPITVQPTEAWPRTSQGPSTRPVEVPGGRAVAAILGLGLVLGLLGPLAILL

ALYLLRRDQRLPPDAHKPPGGGSFRTPIQEEQADAHSTLAKI

SEQ ID NO: 61

MACLGFQRHKAQLNLATRTWPCTLLFFLLFIPVFCKAMHVAQPAVVLASSRGIASFVCE

YASPGKATEVRVTVLRQADSQVTEVCAATYMMGNELTFLDDSICTGTSSGNQVNLTIQ

GLRAMDTGLYICKVELMYPPPYYLGIGNGTQIYVIAKEKKPSYNRGLCENAPNRARM

SEQ ID NO: 62

MACLGFQRHKAQLNLATRTWPCTLLFFLLFIPVFCKAMHVAQPAVVLASSRGIASFVCE

YASPGKATEVRVTVLRQADSQVTEVCAATYMMGNELTFLDDSICTGTSSGNQVNLTIQ

GLRAMDTGLYICKVELMYPPPYYLGIGNGTQIYVIDPEPCPDSDFLLWILAAVSSGLFFY

SFLLTAVSLSKMLKKRSPLTTGVYVKMPPTEPECEKQFQPYFIPIN

SEQ ID NO: 63

MQIPQAPWPVVWAVLQLGWRPGWFLDSPDRPWNPPTFSPALLVVTEGDNATFTCSFSN

TSESFVLNWYRMSPSNQTDKLAAFPEDRSQPGQDCRFRVTQLPNGRDFHMSVVRARRN

DSGTYLCGAISLAPKAQIKESLRAELRVTERRAEVPTAHPSPSPRPAGQFQTLVVGVVGG

LLGSLVLLVWVLAVICSRAARGTIGARRTGQPLKEDPSAVPVFSVDYGELDFQWREKTP

EPPVPCVPEQTEYATIVFPSGMGTSSPARRGSADGPRSAQPLRPEDGHCSWPL

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SEQ ID NO: 64

MAQHGAMGAFRALCGLALLCALSLGQRPTGGPGCGPGRLLLGTGTDARCCRVHTTRC

CRDYPGEECCSEWDCMCVQPEFHCGDPCCTTCRHHPCPPGQGVQSQGKFSFGFQCIDC

ASGTFSGGHEGHCKPWTDCTQFGFLTVFPGNKTHNAVCVPGSPPAEPLGWLTVVLLAV

AACVLLLTSAQLGLHIWQLRSQCMWPRETQLLLEVPPSTEDARSCQFPEEERGERSAEE

KGRLGDLWV

SEQ ID NO: 65

MAQHGAMGAFRALCGLALLCALSLGQRPTGGPGCGPGRLLLGTGTDARCCRVHTTRC

CRDYPGEECCSEWDCMCVQPEFHCGDPCCTTCRHHPCPPGQGVQSQGKFSFGFQCIDC

ASGTFSGGHEGHCKPWTDCCWRCRRRPKTPEAASSPRKSGASDRQRRRGGWETCGCEP

GRPPGPPTAASPSPGAPQAAGALRSALGRALLPWQQKWVQEGGSDQRPGPCSSAAAAG

PCRRERETQSWPPSSLAGP DGVGS

SEQ ID NO: 66

MAQHGAMGAFRALCGLALLCALSLGQRPTGGPGCGPGRLLLGTGTDARCCRVHTTRC

CRDYPGEECCSEWDCMCVQPEFHCGDPCCTTCRHHPCPPGQGVQSQGKFSFGFQCIDC

ASGTFSGGHEGHCKPWTDCTQFGFLTVFPGNKTHNAVCVPGSPPAEPLGWLTVVLLAV

AACVLLLTSAQLGLHIWQLRKTQLLLEVPPSTEDARSCQFPEEERGERSAEEKGRLGDL

WV

(GITR co-stimulatory domain AA)

SEQ ID NO: 67

QLGLHIWQLRSQCMWPRETQLLLEVPPSTEDARSCQFPEEERGERSAEEK

GRLGDLWV

(VH AA)

SEQ ID NO: 68

EVQLVESGGGLVKPGGSLKLSCAASGFKFSRYAMSWVRQTPEKRLEWVATISSGGS

YIYYPDSVKGRFTISRDNVKNTLYLQMSSLRSEDTAMYYCARRDYDLDYFDSWGQ

GTTLTVSS

(VL AA)

SEQ ID NO: 69

DIKMTQSPSSMYASLGERVTITCKASRDIRSYLTWYQQKPWKSPKTLIYYATSLADGVPS

RF SGSGSGQDYSL TISSLESDDTATYYCLQHGESPFTFGSGTKLEIKRA

SEQUENCE LISTING

<160> NUMBER OF SEQ ID NOS: 146

<210> SEQ ID NO 1
<211> LENGTH: 668
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 1

Met Trp Leu Phe Phe Gly Ile Thr Gly Leu Leu Thr Ala Ala Leu Ser
1 5 10 15

Gly His Pro Ser Pro Ala Pro Pro Asp Gln Leu Asn Thr Ser Ser Ala
20 25 30

Glu Ser Glu Leu Trp Glu Pro Gly Glu Arg Leu Pro Val Arg Leu Thr
35 40 45

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Asn Gly Ser Ser Ser Cys Ser Gly Thr Val Glu Val Arg Leu Glu Ala
    50                  55                  60

Ser Trp Glu Pro Ala Cys Gly Ala Leu Trp Asp Ser Arg Ala Ala Glu
65                  70                  75                  80

Ala Val Cys Arg Ala Leu Gly Cys Gly Gly Ala Glu Ala Ala Ser Gln
                85                  90                  95

Leu Ala Pro Pro Thr Pro Glu Leu Pro Pro Pro Pro Ala Ala Gly Asn
            100                 105                 110

Thr Ser Val Ala Ala Asn Ala Thr Leu Ala Gly Ala Pro Ala Leu Leu
        115                 120                 125

Cys Ser Gly Ala Glu Trp Arg Leu Cys Glu Val Val Glu His Ala Cys
    130                 135                 140

Arg Ser Asp Gly Arg Arg Ala Arg Val Thr Cys Ala Glu Asn Arg Ala
145                 150                 155                 160

Leu Arg Leu Val Asp Gly Gly Gly Ala Cys Ala Gly Arg Val Glu Met
                165                 170                 175

Leu Glu His Gly Glu Trp Gly Ser Val Cys Asp Asp Thr Trp Asp Leu
            180                 185                 190

Glu Asp Ala His Val Val Cys Arg Gln Leu Gly Cys Gly Trp Ala Val
        195                 200                 205

Gln Ala Leu Pro Gly Leu His Phe Thr Pro Gly Arg Gly Pro Ile His
    210                 215                 220

Arg Asp Gln Val Asn Cys Ser Gly Ala Glu Ala Tyr Leu Trp Asp Cys
225                 230                 235                 240

Pro Gly Leu Pro Gly Gln His Tyr Cys Gly His Lys Glu Asp Ala Gly
                245                 250                 255

Ala Val Cys Ser Glu His Gln Ser Trp Arg Leu Thr Gly Gly Ala Asp
            260                 265                 270

Arg Cys Glu Gly Gln Val Glu Val His Phe Arg Gly Val Trp Asn Thr
        275                 280                 285

Val Cys Asp Ser Glu Trp Tyr Pro Ser Glu Ala Lys Val Leu Cys Gln
    290                 295                 300

Ser Leu Gly Cys Gly Thr Ala Val Glu Arg Pro Lys Gly Leu Pro His
305                 310                 315                 320

Ser Leu Ser Gly Arg Met Tyr Tyr Ser Cys Asn Gly Glu Glu Leu Thr
                325                 330                 335

Leu Ser Asn Cys Ser Trp Arg Phe Asn Asn Ser Asn Leu Cys Ser Gln
            340                 345                 350

Ser Leu Ala Ala Arg Val Leu Cys Ser Ala Ser Arg Ser Leu His Asn
        355                 360                 365

Leu Ser Thr Pro Glu Val Pro Ala Ser Val Gln Thr Val Thr Ile Glu
    370                 375                 380

Ser Ser Val Thr Val Lys Ile Glu Asn Lys Glu Ser Arg Glu Leu Met
385                 390                 395                 400

Leu Leu Ile Pro Ser Ile Val Leu Gly Ile Leu Leu Leu Gly Ser Leu
                405                 410                 415

Ile Phe Ile Ala Phe Ile Leu Leu Arg Ile Lys Gly Lys Tyr Ala Leu
            420                 425                 430

Pro Val Met Val Asn His Gln His Leu Pro Thr Thr Ile Pro Ala Gly
        435                 440                 445

Ser Asn Ser Tyr Gln Pro Val Pro Ile Thr Ile Pro Lys Glu Val Phe
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    450                 455                 460

Met Leu Pro Ile Gln Val Gln Ala Pro Pro Pro Glu Asp Ser Asp Ser
465                 470                 475                 480

Gly Ser Asp Ser Asp Tyr Glu His Tyr Asp Phe Ser Ala Gln Pro Pro
                485                 490                 495

Val Ala Leu Thr Thr Phe Tyr Asn Ser Gln Arg His Arg Val Thr Asp
            500                 505                 510

Glu Glu Val Gln Gln Ser Arg Phe Gln Met Pro Pro Leu Glu Glu Gly
        515                 520                 525

Leu Glu Glu Leu His Ala Ser His Ile Pro Thr Ala Asn Pro Gly His
    530                 535                 540

Cys Ile Thr Asp Pro Pro Ser Leu Gly Pro Gln Tyr His Pro Arg Ser
545                 550                 555                 560

Asn Ser Glu Ser Ser Thr Ser Ser Gly Glu Asp Tyr Cys Asn Ser Pro
                565                 570                 575

Lys Ser Lys Leu Pro Pro Trp Asn Pro Gln Val Phe Ser Ser Glu Arg
            580                 585                 590

Ser Ser Phe Leu Glu Gln Pro Pro Asn Leu Glu Leu Ala Gly Thr Gln
        595                 600                 605

Pro Ala Phe Ser Ala Gly Pro Pro Ala Asp Asp Ser Ser Ser Thr Ser
    610                 615                 620

Ser Gly Glu Trp Tyr Gln Asn Phe Gln Pro Pro Pro Gln Pro Pro Ser
625                 630                 635                 640

Glu Glu Gln Phe Gly Cys Pro Gly Ser Pro Ser Pro Gln Pro Asp Ser
                645                 650                 655

Thr Asp Asn Asp Asp Tyr Asp Asp Ile Ser Ala Ala
            660                 665


<210> SEQ ID NO 2
<211> LENGTH: 600
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 2

Met Trp Leu Phe Phe Gly Ile Thr Gly Leu Leu Thr Ala Ala Leu Ser
1               5                   10                  15

Gly His Pro Ser Pro Ala Pro Pro Asp Leu Asn Thr Ser Ser Ala Glu
            20                  25                  30

Ser Glu Leu Trp Glu Pro Gly Glu Arg Leu Pro Val Arg Leu Thr Asn
        35                  40                  45

Gly Ser Ser Ser Cys Ser Gly Thr Val Glu Val Arg Leu Glu Ala Ser
    50                  55                  60

Trp Glu Pro Ala Cys Gly Ala Leu Trp Asp Ser Arg Ala Ala Glu Ala
65                  70                  75                  80

Val Cys Arg Ala Leu Gly Cys Gly Gly Ala Glu Ala Ala Ser Gln Leu
                85                  90                  95

Ala Pro Pro Thr Pro Glu Leu Pro Pro Pro Pro Ala Ala Gly Asn Thr
            100                 105                 110

Ser Val Ala Ala Asn Ala Thr Leu Ala Gly Ala Pro Ala Leu Leu Cys
        115                 120                 125

Ser Gly Ala Glu Trp Arg Leu Cys Glu Val Val Glu His Ala Cys Arg
    130                 135                 140
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Ser Asp Gly Arg Arg Ala Arg Val Thr Cys Ala Glu Asn Arg Ala Leu
145                 150                 155                 160

Arg Leu Val Asp Gly Gly Gly Ala Cys Ala Gly Arg Val Glu Met Leu
                165                 170                 175

Glu His Gly Glu Trp Gly Ser Val Cys Asp Asp Thr Trp Asp Leu Glu
            180                 185                 190

Asp Ala His Val Val Cys Arg Gln Leu Gly Cys Gly Trp Ala Val Gln
        195                 200                 205

Ala Leu Pro Gly Leu His Phe Thr Pro Gly Arg Gly Pro Ile His Arg
    210                 215                 220

Asp Gln Val Asn Cys Ser Gly Ala Glu Ala Tyr Leu Trp Asp Cys Pro
225                 230                 235                 240

Gly Leu Pro Gly Gln His Tyr Cys Gly His Lys Glu Asp Ala Gly Ala
                245                 250                 255

Val Cys Ser Glu His Gln Ser Trp Arg Leu Thr Gly Gly Ala Asp Arg
            260                 265                 270

Cys Glu Gly Gln Val Glu Val His Phe Arg Gly Val Trp Asn Thr Val
        275                 280                 285

Cys Asp Ser Glu Trp Tyr Pro Ser Glu Ala Lys Val Leu Cys Gln Ser
    290                 295                 300

Leu Gly Cys Gly Thr Ala Val Glu Arg Pro Lys Gly Leu Pro His Ser
305                 310                 315                 320

Leu Ser Gly Arg Met Tyr Tyr Ser Cys Asn Gly Glu Glu Leu Thr Leu
                325                 330                 335

Ser Asn Cys Ser Trp Arg Phe Asn Asn Ser Asn Leu Cys Ser Gln Ser
            340                 345                 350

Leu Ala Ala Arg Val Leu Cys Ser Ala Ser Arg Ser Leu His Asn Leu
        355                 360                 365

Ser Thr Pro Glu Val Pro Ala Ser Val Gln Thr Val Thr Ile Glu Ser
    370                 375                 380

Ser Val Thr Val Lys Ile Glu Asn Lys Glu Ser Arg Glu Leu Met Leu
385                 390                 395                 400

Leu Ile Pro Ser Ile Val Leu Gly Ile Leu Leu Leu Gly Ser Leu Ile
                405                 410                 415

Phe Ile Ala Phe Ile Leu Leu Arg Ile Lys Gly Lys Tyr Val Phe Met
            420                 425                 430

Leu Pro Ile Gln Val Gln Ala Pro Pro Pro Glu Asp Ser Asp Ser Gly
        435                 440                 445

Ser Asp Ser Asp Tyr Glu His Tyr Asp Phe Ser Ala Gln Pro Pro Val
    450                 455                 460

Ala Leu Thr Thr Phe Tyr Asn Ser Gln Arg His Arg Val Thr Asp Glu
465                 470                 475                 480

Glu Val Gln Gln Ser Arg Phe Gln Met Pro Pro Leu Glu Glu Gly Leu
                485                 490                 495

Glu Glu Leu His Ala Ser His Ile Pro Thr Ala Asn Pro Gly His Cys
            500                 505                 510

Ile Thr Asp Pro Pro Ser Leu Gly Pro Gln Tyr His Pro Arg Ser Asn
        515                 520                 525

Ser Glu Ser Ser Thr Ser Ser Gly Glu Asp Tyr Cys Asn Ser Pro Lys
    530                 535                 540

Ser Lys Leu Pro Pro Trp Asn Pro Gln Val Phe Ser Ser Glu Arg Ser
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545                 550                 555                 560

Ser Phe Leu Glu Gln Pro Pro Asn Leu Glu Leu Ala Gly Thr Gln Pro
                565                 570                 575

Ala Phe Ser Gly Ser Pro Ser Pro Gln Pro Asp Ser Thr Asp Asn Asp
            580                 585                 590

Asp Tyr Asp Asp Ile Ser Ala Ala
        595                 600


<210> SEQ ID NO 3
<211> LENGTH: 592
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 3

Met Trp Leu Phe Phe Gly Ile Thr Gly Leu Leu Thr Ala Ala Leu Ser
1               5                   10                  15

Gly His Pro Ser Pro Ala Pro Pro Asp Gln Leu Asn Thr Ser Ser Ala
            20                  25                  30

Glu Ser Glu Leu Trp Glu Pro Gly Glu Arg Leu Pro Val Arg Leu Thr
        35                  40                  45

Asn Gly Ser Ser Ser Cys Ser Gly Thr Val Glu Val Arg Leu Glu Ala
    50                  55                  60

Ser Trp Glu Pro Ala Cys Gly Ala Leu Trp Asp Ser Arg Ala Ala Glu
65                  70                  75                  80

Ala Val Cys Arg Ala Leu Gly Cys Gly Gly Ala Glu Ala Ala Ser Gln
                85                  90                  95

Leu Ala Pro Pro Thr Pro Glu Leu Pro Pro Pro Pro Ala Ala Gly Asn
            100                 105                 110

Thr Ser Val Ala Ala Asn Ala Thr Leu Ala Gly Ala Pro Ala Leu Leu
        115                 120                 125

Cys Ser Gly Ala Glu Trp Arg Leu Cys Glu Val Val Glu His Ala Cys
    130                 135                 140

Arg Ser Asp Gly Arg Arg Ala Arg Val Thr Cys Ala Glu Asn Arg Ala
145                 150                 155                 160

Leu Arg Leu Val Asp Gly Gly Gly Ala Cys Ala Gly Arg Val Glu Met
                165                 170                 175

Leu Glu His Gly Glu Trp Gly Ser Val Cys Asp Asp Thr Trp Asp Leu
            180                 185                 190

Glu Asp Ala His Val Val Cys Arg Gln Leu Gly Cys Gly Trp Ala Val
        195                 200                 205

Gln Ala Leu Pro Gly Leu His Phe Thr Pro Gly Arg Gly Pro Ile His
    210                 215                 220

Arg Asp Gln Val Asn Cys Ser Gly Ala Glu Ala Tyr Leu Trp Asp Cys
225                 230                 235                 240

Pro Gly Leu Pro Gly Gln His Tyr Cys Gly His Lys Glu Asp Ala Gly
                245                 250                 255

Ala Val Cys Ser Glu His Gln Ser Trp Arg Leu Thr Gly Gly Ala Asp
            260                 265                 270

Arg Cys Glu Gly Gln Val Glu Val His Phe Arg Gly Val Trp Asn Thr
        275                 280                 285

Val Cys Asp Ser Glu Trp Tyr Pro Ser Glu Ala Lys Val Leu Cys Gln
    290                 295                 300
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Ser Leu Gly Cys Gly Thr Ala Val Glu Arg Pro Lys Gly Leu Pro His
305                 310                 315                 320

Ser Leu Ser Gly Arg Met Tyr Tyr Ser Cys Asn Gly Glu Glu Leu Thr
                325                 330                 335

Leu Ser Asn Cys Ser Trp Arg Phe Asn Asn Ser Asn Leu Cys Ser Gln
            340                 345                 350

Ser Leu Ala Ala Arg Val Leu Cys Ser Ala Ser Arg Ser Leu His Asn
        355                 360                 365

Leu Ser Thr Pro Glu Val Pro Ala Ser Val Gln Thr Val Thr Ile Glu
    370                 375                 380

Ser Ser Val Thr Val Lys Ile Glu Asn Lys Glu Ser Arg Glu Leu Met
385                 390                 395                 400

Leu Leu Ile Pro Ser Ile Val Leu Gly Ile Leu Leu Leu Gly Ser Leu
                405                 410                 415

Ile Phe Ile Ala Phe Ile Leu Leu Arg Ile Lys Gly Lys Tyr Ala Leu
            420                 425                 430

Pro Val Met Val Asn His Gln His Leu Pro Thr Thr Ile Pro Ala Gly
        435                 440                 445

Ser Asn Ser Tyr Gln Pro Val Pro Ile Thr Ile Pro Lys Glu Asp Ser
    450                 455                 460

Gln Arg His Arg Val Thr Asp Glu Glu Val Gln Gln Ser Arg Phe Gln
465                 470                 475                 480

Met Pro Pro Leu Glu Glu Gly Leu Glu Glu Leu His Ala Ser His Ile
                485                 490                 495

Pro Thr Ala Asn Pro Gly His Cys Ile Thr Asp Pro Pro Ser Leu Gly
            500                 505                 510

Pro Gln Tyr His Pro Arg Ser Asn Ser Glu Ser Ser Thr Ser Ser Gly
        515                 520                 525

Glu Asp Tyr Cys Asn Ser Pro Lys Ser Lys Leu Pro Pro Trp Asn Pro
    530                 535                 540

Gln Val Phe Ser Ser Glu Arg Ser Ser Phe Leu Glu Gln Pro Pro Asn
545                 550                 555                 560

Leu Glu Leu Ala Gly Thr Gln Pro Ala Phe Ser Gly Ser Pro Ser Pro
                565                 570                 575

Gln Pro Asp Ser Thr Asp Asn Asp Asp Tyr Asp Asp Ile Ser Ala Ala
            580                 585                 590


<210> SEQ ID NO 4
<211> LENGTH: 123
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 4

Met Leu Arg Leu Leu Leu Ala Leu Asn Leu Phe Pro Ser Ile Gln Val
1               5                   10                  15

Thr Gly Asn Lys Ile Leu Val Lys Gln Ser Pro Met Leu Val Ala Tyr
            20                  25                  30

Asp Asn Ala Val Asn Leu Ser Trp Lys His Leu Cys Pro Ser Pro Leu
        35                  40                  45

Phe Pro Gly Pro Ser Lys Pro Phe Trp Val Leu Val Val Val Gly Gly
    50                  55                  60

Val Leu Ala Cys Tyr Ser Leu Leu Val Thr Val Ala Phe Ile Ile Phe
65                  70                  75                  80
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Trp Val Arg Ser Lys Arg Ser Arg Leu Leu His Ser Asp Tyr Met Asn
                85                  90                  95

Met Thr Pro Arg Arg Pro Gly Pro Thr Arg Lys His Tyr Gln Pro Tyr
            100                 105                 110

Ala Pro Pro Arg Asp Phe Ala Ala Tyr Arg Ser
        115                 120


<210> SEQ ID NO 5
<211> LENGTH: 220
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 5

Met Leu Arg Leu Leu Leu Ala Leu Asn Leu Phe Pro Ser Ile Gln Val
1               5                   10                  15

Thr Gly Asn Lys Ile Leu Val Lys Gln Ser Pro Met Leu Val Ala Tyr
            20                  25                  30

Asp Asn Ala Val Asn Leu Ser Cys Lys Tyr Ser Tyr Asn Leu Phe Ser
        35                  40                  45

Arg Glu Phe Arg Ala Ser Leu His Lys Gly Leu Asp Ser Ala Val Glu
    50                  55                  60

Val Cys Val Val Tyr Gly Asn Tyr Ser Gln Gln Leu Gln Val Tyr Ser
65                  70                  75                  80

Lys Thr Gly Phe Asn Cys Asp Gly Lys Leu Gly Asn Glu Ser Val Thr
                85                  90                  95

Phe Tyr Leu Gln Asn Leu Tyr Val Asn Gln Thr Asp Ile Tyr Phe Cys
            100                 105                 110

Lys Ile Glu Val Met Tyr Pro Pro Pro Tyr Leu Asp Asn Glu Lys Ser
        115                 120                 125

Asn Gly Thr Ile Ile His Val Lys Gly Lys His Leu Cys Pro Ser Pro
    130                 135                 140

Leu Phe Pro Gly Pro Ser Lys Pro Phe Trp Val Leu Val Val Val Gly
145                 150                 155                 160

Gly Val Leu Ala Cys Tyr Ser Leu Leu Val Thr Val Ala Phe Ile Ile
                165                 170                 175

Phe Trp Val Arg Ser Lys Arg Ser Arg Leu Leu His Ser Asp Tyr Met
            180                 185                 190

Asn Met Thr Pro Arg Arg Pro Gly Pro Thr Arg Lys His Tyr Gln Pro
        195                 200                 205

Tyr Ala Pro Pro Arg Asp Phe Ala Ala Tyr Arg Ser
    210                 215                 220


<210> SEQ ID NO 6
<211> LENGTH: 220
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 6

Met Leu Arg Leu Leu Leu Ala Leu Asn Leu Phe Pro Ser Ile Gln Val
1               5                   10                  15

Thr Gly Asn Lys Ile Leu Val Lys Gln Ser Pro Met Leu Val Ala Tyr
            20                  25                  30

Asp Asn Ala Val Asn Leu Ser Cys Lys Tyr Ser Tyr Asn Leu Phe Ser
        35                  40                  45
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Arg Glu Phe Arg Ala Ser Leu His Lys Gly Leu Asp Ser Ala Val Glu
    50                  55                  60

Val Cys Val Val Tyr Gly Asn Tyr Ser Gln Gln Leu Gln Val Tyr Ser
65                  70                  75                  80

Lys Thr Gly Phe Asn Cys Asp Gly Lys Leu Gly Asn Glu Ser Val Thr
                85                  90                  95

Phe Tyr Leu Gln Asn Leu Tyr Val Asn Gln Thr Asp Ile Tyr Phe Cys
            100                 105                 110

Lys Ile Glu Val Met Tyr Pro Pro Pro Tyr Leu Asp Asn Glu Lys Ser
        115                 120                 125

Asn Gly Thr Ile Ile His Val Lys Gly Lys His Leu Cys Pro Ser Pro
    130                 135                 140

Leu Phe Pro Gly Pro Ser Lys Pro Phe Trp Val Leu Val Val Val Gly
145                 150                 155                 160

Gly Val Leu Ala Cys Tyr Ser Leu Leu Val Thr Val Ala Phe Ile Ile
                165                 170                 175

Phe Trp Val Arg Ser Lys Arg Ser Arg Leu Leu His Ser Asp Tyr Met
            180                 185                 190

Asn Met Thr Pro Arg Arg Pro Gly Pro Thr Arg Lys His Tyr Gln Pro
        195                 200                 205

Tyr Ala Pro Pro Arg Asp Phe Ala Ala Tyr Arg Ser
    210                 215                 220


<210> SEQ ID NO 7
<211> LENGTH: 41
<212> TYPE: PRT
<213> ORGANISM: Unknown
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Unknown:
      CD28 GG sequence"

<400> SEQUENCE: 7

Arg Ser Lys Arg Ser Arg Gly Gly His Ser Asp Tyr Met Asn Met Thr
1               5                   10                  15

Pro Arg Arg Pro Gly Pro Thr Arg Lys His Tyr Gln Pro Tyr Ala Pro
            20                  25                  30

Pro Arg Asp Phe Ala Ala Tyr Arg Ser
        35                  40


<210> SEQ ID NO 8
<211> LENGTH: 41
<212> TYPE: PRT
<213> ORGANISM: Unknown
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Unknown:
      CD28 LL sequence"

<400> SEQUENCE: 8

Arg Ser Lys Arg Ser Arg Leu Leu His Ser Asp Tyr Met Asn Met Thr
1               5                   10                  15

Pro Arg Arg Pro Gly Pro Thr Arg Lys His Tyr Gln Pro Tyr Ala Pro
            20                  25                  30

Pro Arg Asp Phe Ala Ala Tyr Arg Ser
        35                  40
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<210> SEQ ID NO 9
<211> LENGTH: 458
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 9

Met Asn Arg Gly Val Pro Phe Arg His Leu Leu Leu Val Leu Gln Leu
1 5 10 15

Ala Leu Leu Pro Ala Ala Thr Gln Gly Lys Lys Val Val Leu Gly Lys
20 25 30

Lys Gly Asp Thr Val Glu Leu Thr Cys Thr Ala Ser Gln Lys Lys Ser
35 40 45

Ile Gln Phe His Trp Lys Asn Ser Asn Gln Ile Lys Ile Leu Gly Asn
50 55 60

Gln Gly Ser Phe Leu Thr Lys Gly Pro Ser Lys Leu Asn Asp Arg Ala
65 70 75 80

Asp Ser Arg Arg Ser Leu Trp Asp Gln Gly Asn Phe Pro Leu Ile Ile
85 90 95

Lys Asn Leu Lys Ile Glu Asp Ser Asp Thr Tyr Ile Cys Glu Val Glu
100 105 110

Asp Gln Lys Glu Glu Val Gln Leu Leu Val Phe Gly Leu Thr Ala Asn
115 120 125

Ser Asp Thr His Leu Leu Gln Gly Gln Ser Leu Thr Leu Thr Leu Glu
130 135 140

Ser Pro Pro Gly Ser Ser Pro Ser Val Gln Cys Arg Ser Pro Arg Gly
145 150 155 160

Lys Asn Ile Gln Gly Gly Lys Thr Leu Ser Val Ser Gln Leu Glu Leu
165 170 175

Gln Asp Ser Gly Thr Trp Thr Cys Thr Val Leu Gln Asn Gln Lys Lys
180 185 190

Val Glu Phe Lys Ile Asp Ile Val Val Leu Ala Phe Gln Lys Ala Ser
195 200 205

Ser Ile Val Tyr Lys Lys Glu Gly Glu Gln Val Glu Phe Ser Phe Pro
210 215 220

Leu Ala Phe Thr Val Glu Lys Leu Thr Gly Ser Gly Glu Leu Trp Trp
225 230 235 240

Gln Ala Glu Arg Ala Ser Ser Ser Lys Ser Trp Ile Thr Phe Asp Leu
245 250 255

Lys Asn Lys Glu Val Ser Val Lys Arg Val Thr Gln Asp Pro Lys Leu
260 265 270

Gln Met Gly Lys Lys Leu Pro Leu His Leu Thr Leu Pro Gln Ala Leu
275 280 285

Pro Gln Tyr Ala Gly Ser Gly Asn Leu Thr Leu Ala Leu Glu Ala Lys
290 295 300

Thr Gly Lys Leu His Gln Glu Val Asn Leu Val Val Met Arg Ala Thr
305 310 315 320

Gln Leu Gln Lys Asn Leu Thr Cys Glu Val Trp Gly Pro Thr Ser Pro
325 330 335

Lys Leu Met Leu Ser Leu Lys Leu Glu Asn Lys Glu Ala Lys Val Ser
340 345 350

Lys Arg Glu Lys Ala Val Trp Val Leu Asn Pro Glu Ala Gly Met Trp
355 360 365

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Gln Cys Leu Leu Ser Asp Ser Gly Gln Val Leu Leu Glu Ser Asn Ile
    370                 375                 380

Lys Val Leu Pro Thr Trp Ser Thr Pro Val Gln Pro Met Ala Leu Ile
385                 390                 395                 400

Val Leu Gly Gly Val Ala Gly Leu Leu Leu Phe Ile Gly Leu Gly Ile
                405                 410                 415

Phe Phe Cys Val Arg Cys Arg His Arg Arg Arg Gln Ala Glu Arg Met
            420                 425                 430

Ser Gln Ile Lys Arg Leu Leu Ser Glu Lys Lys Thr Cys Gln Cys Pro
        435                 440                 445

His Arg Phe Gln Lys Thr Cys Ser Pro Ile
    450                 455


<210> SEQ ID NO 10
<211> LENGTH: 279
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 10

Met Pro Thr Pro Leu Val His Pro His Leu Pro Ile Ser Ser Pro Arg
1               5                   10                  15

Val Ser Pro Phe Pro Pro Pro Ala Phe Gln Lys Ala Ser Ser Ile Val
            20                  25                  30

Tyr Lys Lys Glu Gly Glu Gln Val Glu Phe Ser Phe Pro Leu Ala Phe
        35                  40                  45

Thr Val Glu Lys Leu Thr Gly Ser Gly Glu Leu Trp Trp Gln Ala Glu
    50                  55                  60

Arg Ala Ser Ser Ser Lys Ser Trp Ile Thr Phe Asp Leu Lys Asn Lys
65                  70                  75                  80

Glu Val Ser Val Lys Arg Val Thr Gln Asp Pro Lys Leu Gln Met Gly
                85                  90                  95

Lys Lys Leu Pro Leu His Leu Thr Leu Pro Gln Ala Leu Pro Gln Tyr
            100                 105                 110

Ala Gly Ser Gly Asn Leu Thr Leu Ala Leu Glu Ala Lys Thr Gly Lys
        115                 120                 125

Leu His Gln Glu Val Asn Leu Val Val Met Arg Ala Thr Gln Leu Gln
    130                 135                 140

Lys Asn Leu Thr Cys Glu Val Trp Gly Pro Thr Ser Pro Lys Leu Met
145                 150                 155                 160

Leu Ser Leu Lys Leu Glu Asn Lys Glu Ala Lys Val Ser Lys Arg Glu
                165                 170                 175

Lys Ala Val Trp Val Leu Asn Pro Glu Ala Gly Met Trp Gln Cys Leu
            180                 185                 190

Leu Ser Asp Ser Gly Gln Val Leu Leu Glu Ser Asn Ile Lys Val Leu
        195                 200                 205

Pro Thr Trp Ser Thr Pro Val Gln Pro Met Ala Leu Ile Val Leu Gly
    210                 215                 220

Gly Val Ala Gly Leu Leu Leu Phe Ile Gly Leu Gly Ile Phe Phe Cys
225                 230                 235                 240

Val Arg Cys Arg His Arg Arg Arg Gln Ala Glu Arg Met Ser Gln Ile
                245                 250                 255

Lys Arg Leu Leu Ser Glu Lys Lys Thr Cys Gln Cys Pro His Arg Phe
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            260                 265                 270

Gln Lys Thr Cys Ser Pro Ile
        275


<210> SEQ ID NO 11
<211> LENGTH: 185
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 11

Met Gly Lys Lys Leu Pro Leu His Leu Thr Leu Pro Gln Ala Leu Pro
1               5                   10                  15

Gln Tyr Ala Gly Ser Gly Asn Leu Thr Leu Ala Leu Glu Ala Lys Thr
            20                  25                  30

Gly Lys Leu His Gln Glu Val Asn Leu Val Val Met Arg Ala Thr Gln
        35                  40                  45

Leu Gln Lys Asn Leu Thr Cys Glu Val Trp Gly Pro Thr Ser Pro Lys
    50                  55                  60

Leu Met Leu Ser Leu Lys Leu Glu Asn Lys Glu Ala Lys Val Ser Lys
65                  70                  75                  80

Arg Glu Lys Ala Val Trp Val Leu Asn Pro Glu Ala Gly Met Trp Gln
                85                  90                  95

Cys Leu Leu Ser Asp Ser Gly Gln Val Leu Leu Glu Ser Asn Ile Lys
            100                 105                 110

Val Leu Pro Thr Trp Ser Thr Pro Val Gln Pro Met Ala Leu Ile Val
        115                 120                 125

Leu Gly Gly Val Ala Gly Leu Leu Leu Phe Ile Gly Leu Gly Ile Phe
    130                 135                 140

Phe Cys Val Arg Cys Arg His Arg Arg Arg Gln Ala Glu Arg Met Ser
145                 150                 155                 160

Gln Ile Lys Arg Leu Leu Ser Glu Lys Lys Thr Cys Gln Cys Pro His
                165                 170                 175

Arg Phe Gln Lys Thr Cys Ser Pro Ile
            180                 185


<210> SEQ ID NO 12
<211> LENGTH: 185
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 12

Met Gly Lys Lys Leu Pro Leu His Leu Thr Leu Pro Gln Ala Leu Pro
1               5                   10                  15

Gln Tyr Ala Gly Ser Gly Asn Leu Thr Leu Ala Leu Glu Ala Lys Thr
            20                  25                  30

Gly Lys Leu His Gln Glu Val Asn Leu Val Val Met Arg Ala Thr Gln
        35                  40                  45

Leu Gln Lys Asn Leu Thr Cys Glu Val Trp Gly Pro Thr Ser Pro Lys
    50                  55                  60

Leu Met Leu Ser Leu Lys Leu Glu Asn Lys Glu Ala Lys Val Ser Lys
65                  70                  75                  80

Arg Glu Lys Ala Val Trp Val Leu Asn Pro Glu Ala Gly Met Trp Gln
                85                  90                  95

Cys Leu Leu Ser Asp Ser Gly Gln Val Leu Leu Glu Ser Asn Ile Lys
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            100                 105                 110

Val Leu Pro Thr Trp Ser Thr Pro Val Gln Pro Met Ala Leu Ile Val
        115                 120                 125

Leu Gly Gly Val Ala Gly Leu Leu Leu Phe Ile Gly Leu Gly Ile Phe
    130                 135                 140

Phe Cys Val Arg Cys Arg His Arg Arg Arg Gln Ala Glu Arg Met Ser
145                 150                 155                 160

Gln Ile Lys Arg Leu Leu Ser Glu Lys Lys Thr Cys Gln Cys Pro His
                165                 170                 175

Arg Phe Gln Lys Thr Cys Ser Pro Ile
            180                 185


<210> SEQ ID NO 13
<211> LENGTH: 185
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 13

Met Gly Lys Lys Leu Pro Leu His Leu Thr Leu Pro Gln Ala Leu Pro
1               5                   10                  15

Gln Tyr Ala Gly Ser Gly Asn Leu Thr Leu Ala Leu Glu Ala Lys Thr
            20                  25                  30

Gly Lys Leu His Gln Glu Val Asn Leu Val Val Met Arg Ala Thr Gln
        35                  40                  45

Leu Gln Lys Asn Leu Thr Cys Glu Val Trp Gly Pro Thr Ser Pro Lys
    50                  55                  60

Leu Met Leu Ser Leu Lys Leu Glu Asn Lys Glu Ala Lys Val Ser Lys
65                  70                  75                  80

Arg Glu Lys Ala Val Trp Val Leu Asn Pro Glu Ala Gly Met Trp Gln
                85                  90                  95

Cys Leu Leu Ser Asp Ser Gly Gln Val Leu Leu Glu Ser Asn Ile Lys
            100                 105                 110

Val Leu Pro Thr Trp Ser Thr Pro Val Gln Pro Met Ala Leu Ile Val
        115                 120                 125

Leu Gly Gly Val Ala Gly Leu Leu Leu Phe Ile Gly Leu Gly Ile Phe
    130                 135                 140

Phe Cys Val Arg Cys Arg His Arg Arg Arg Gln Ala Glu Arg Met Ser
145                 150                 155                 160

Gln Ile Lys Arg Leu Leu Ser Glu Lys Lys Thr Cys Gln Cys Pro His
                165                 170                 175

Arg Phe Gln Lys Thr Cys Ser Pro Ile
            180                 185


<210> SEQ ID NO 14
<211> LENGTH: 42
<212> TYPE: PRT
<213> ORGANISM: Unknown
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Unknown:
      4-1BB sequence"

<400> SEQUENCE: 14

Lys Arg Gly Arg Lys Lys Leu Leu Tyr Ile Phe Lys Gln Pro Phe Met
1               5                   10                  15
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Arg Pro Val Gln Thr Thr Gln Glu Glu Asp Gly Cys Ser Cys Arg Phe
            20                  25                  30

Pro Glu Glu Glu Glu Gly Gly Cys Glu Leu
        35                  40


<210> SEQ ID NO 15
<211> LENGTH: 255
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 15

Met Gly Asn Ser Cys Tyr Asn Ile Val Ala Thr Leu Leu Leu Val Leu
1               5                   10                  15

Asn Phe Glu Arg Thr Arg Ser Leu Gln Asp Pro Cys Ser Asn Cys Pro
            20                  25                  30

Ala Gly Thr Phe Cys Asp Asn Asn Arg Asn Gln Ile Cys Ser Pro Cys
        35                  40                  45

Pro Pro Asn Ser Phe Ser Ser Ala Gly Gly Gln Arg Thr Cys Asp Ile
    50                  55                  60

Cys Arg Gln Cys Lys Gly Val Phe Arg Thr Arg Lys Glu Cys Ser Ser
65                  70                  75                  80

Thr Ser Asn Ala Glu Cys Asp Cys Thr Pro Gly Phe His Cys Leu Gly
                85                  90                  95

Ala Gly Cys Ser Met Cys Glu Gln Asp Cys Lys Gln Gly Gln Glu Leu
            100                 105                 110

Thr Lys Lys Gly Cys Lys Asp Cys Cys Phe Gly Thr Phe Asn Asp Gln
        115                 120                 125

Lys Arg Gly Ile Cys Arg Pro Trp Thr Asn Cys Ser Leu Asp Gly Lys
    130                 135                 140

Ser Val Leu Val Asn Gly Thr Lys Glu Arg Asp Val Val Cys Gly Pro
145                 150                 155                 160

Ser Pro Ala Asp Leu Ser Pro Gly Ala Ser Ser Val Thr Pro Pro Ala
                165                 170                 175

Pro Ala Arg Glu Pro Gly His Ser Pro Gln Ile Ile Ser Phe Phe Leu
            180                 185                 190

Ala Leu Thr Ser Thr Ala Leu Leu Phe Leu Leu Phe Phe Leu Thr Leu
        195                 200                 205

Arg Phe Ser Val Val Lys Arg Gly Arg Lys Lys Leu Leu Tyr Ile Phe
    210                 215                 220

Lys Gln Pro Phe Met Arg Pro Val Gln Thr Thr Gln Glu Glu Asp Gly
225                 230                 235                 240

Cys Ser Cys Arg Phe Pro Glu Glu Glu Glu Gly Gly Cys Glu Leu
                245                 250                 255


<210> SEQ ID NO 16
<211> LENGTH: 199
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 16

Met Lys Ser Gly Leu Trp Tyr Phe Phe Leu Phe Cys Leu Arg Ile Lys
1               5                   10                  15

Val Leu Thr Gly Glu Ile Asn Gly Ser Ala Asn Tyr Glu Met Phe Ile
            20                  25                  30
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Phe His Asn Gly Gly Val Gln Ile Leu Cys Lys Tyr Pro Asp Ile Val
        35                  40                  45

Gln Gln Phe Lys Met Gln Leu Leu Lys Gly Gly Gln Ile Leu Cys Asp
    50                  55                  60

Leu Thr Lys Thr Lys Gly Ser Gly Asn Thr Val Ser Ile Lys Ser Leu
65                  70                  75                  80

Lys Phe Cys His Ser Gln Leu Ser Asn Asn Ser Val Ser Phe Phe Leu
                85                  90                  95

Tyr Asn Leu Asp His Ser His Ala Asn Tyr Tyr Phe Cys Asn Leu Ser
            100                 105                 110

Ile Phe Asp Pro Pro Pro Phe Lys Val Thr Leu Thr Gly Gly Tyr Leu
        115                 120                 125

His Ile Tyr Glu Ser Gln Leu Cys Cys Gln Leu Lys Phe Trp Leu Pro
    130                 135                 140

Ile Gly Cys Ala Ala Phe Val Val Val Cys Ile Leu Gly Cys Ile Leu
145                 150                 155                 160

Ile Cys Trp Leu Thr Lys Lys Lys Tyr Ser Ser Ser Val His Asp Pro
                165                 170                 175

Asn Gly Glu Tyr Met Phe Met Arg Ala Val Asn Thr Ala Lys Lys Ser
            180                 185                 190

Arg Leu Thr Asp Val Thr Leu
        195


<210> SEQ ID NO 17
<211> LENGTH: 41
<212> TYPE: PRT
<213> ORGANISM: Unknown
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Unknown:
      CTLA-4 sequence"

<400> SEQUENCE: 17

Ala Val Ser Leu Ser Lys Met Leu Lys Lys Arg Ser Pro Leu Thr Thr
1               5                   10                  15

Gly Val Tyr Val Lys Met Pro Pro Thr Glu Pro Glu Cys Glu Lys Gln
            20                  25                  30

Phe Gln Pro Tyr Phe Ile Pro Ile Asn
        35                  40


<210> SEQ ID NO 18
<211> LENGTH: 327
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
      Synthetic polynucleotide"

<400> SEQUENCE: 18

gacatccaaa tgacacaaag tcctagctct ctctcagcaa gtgttggcga ccgtgtgacc     60

atcacatgta aagcttcaag ggatattcgc agctacctga cttggtacca acaaaagccc    120

ggaaaagcgc ctaaaacgct tatttactat gccaccagcc tcgcagatgg tgtcccctcc    180

agattttctg gatcgggatc agggcaagat tatagtctta cgatatcgag tcttgagtcg    240

gacgatactg ccacatacta ctgcttacag cacggggaaa gcccattcac attcggaagt    300
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ggtacgaaac tcgagatcaa acgggca 327

<210> SEQ ID NO 19
<211> LENGTH: 357
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic polynucleotide"

<400> SEQUENCE: 19

gaagtccaat tggtcgagag cggaggtggg cttgttaaac caggaggcag tttaaaatta 60

tcatgtgctg cctcgggttt caagttctcg cggtatgcta tgtcctgggt acgccaagca 120

cctggaaagc gtttagaatg ggtggccaca attagtagtg gtggttcata tatatattat 180

cccgactccg tcaaaggaag gttcacgatt tcaagggaca atgtgaagaa caccctctac 240

ttacagatga gtagtctgcg ttctgaggat accgctatgt actactgtgc tcggagagat 300

tacgatctgg attatttcga cagctggggt cagggcacac tcgttacagt atcctcg 357

<210> SEQ ID NO 20
<211> LENGTH: 60
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"

<400> SEQUENCE: 20

gtccaacttg ttgaatcagg tgggggggctg gtcaaacccg ggggctctct gaaactaagt 60

<210> SEQ ID NO 21
<211> LENGTH: 45
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"

<400> SEQUENCE: 21

ttctctcggt acgctatgtc gtgggtcaga caagcgcccg gcaaa 45

<210> SEQ ID NO 22
<211> LENGTH: 57
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"

<400> SEQUENCE: 22

cgtgattatg atctagacta ctttgactcc tggggtcaag gtacgctcgt gacggtt 57

<210> SEQ ID NO 23
<211> LENGTH: 22
<212> TYPE: PRT
<213> ORGANISM: Unknown
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Unknown:

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CD4 transmembrane sequence"

<400> SEQUENCE: 23

Met Ala Leu Ile Val Leu Gly Gly Val Ala Gly Leu Leu Leu Phe Ile
1 5 10 15

Gly Leu Gly Ile Phe Phe
20

<210> SEQ ID NO 24
<211> LENGTH: 66
<212> TYPE: DNA
<213> ORGANISM: Unknown
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Unknown:
CD4 transmembrane NA sequence"

<400> SEQUENCE: 24

atggccctga ttgtgctggg gggcgtcgcc ggcctcctgc ttttcattgg gctaggcatc 60

ttcttc 66

<210> SEQ ID NO 25
<211> LENGTH: 21
<212> TYPE: PRT
<213> ORGANISM: Unknown
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Unknown:
CD8 transmembrane sequence"

<400> SEQUENCE: 25

Ile Tyr Ile Trp Ala Pro Leu Ala Gly Thr Cys Gly Val Leu Leu Leu
1 5 10 15

Ser Leu Val Ile Thr
20

<210> SEQ ID NO 26
<211> LENGTH: 54
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"

<400> SEQUENCE: 26

gggtcaacgt cgggcggggg ttccggtgga ggaagtggag gtggtggaag ttct 54

<210> SEQ ID NO 27
<211> LENGTH: 60
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"

<400> SEQUENCE: 27

ggcggcggcg gaagtggcgg cggcggctca ggcgggggggg gttctggggg cggcggttca 60

<210> SEQ ID NO 28
<211> LENGTH: 20
<212> TYPE: PRT

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<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic peptide"

<400> SEQUENCE: 28

Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Lys Pro Gly Gly Ser
1 5 10 15

Leu Lys Leu Ser
20

<210> SEQ ID NO 29
<211> LENGTH: 15
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic peptide"

<400> SEQUENCE: 29

Phe Ser Arg Tyr Ala Met Ser Trp Val Arg Gln Ala Pro Gly Lys
1 5 10 15

<210> SEQ ID NO 30
<211> LENGTH: 19
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic peptide"

<400> SEQUENCE: 30

Arg Asp Tyr Asp Leu Asp Tyr Phe Asp Ser Trp Gly Gln Gly Thr Leu
1 5 10 15

Val Thr Val

<210> SEQ ID NO 31
<211> LENGTH: 38
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic polypeptide"

<400> SEQUENCE: 31

Cys Trp Leu Thr Lys Lys Lys Tyr Ser Ser Ser Val His Asp Pro Asn
1 5 10 15

Gly Glu Tyr Met Phe Met Arg Ala Val Asn Thr Ala Lys Lys Ser Arg
20 25 30

Leu Thr Asp Val Thr Leu
35

<210> SEQ ID NO 32
<211> LENGTH: 42
<212> TYPE: PRT
<213> ORGANISM: Unknown
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Unknown:
OX-40 sequence"

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<400> SEQUENCE: 32

Ala Leu Tyr Leu Leu Arg Arg Asp Gln Arg Leu Pro Pro Asp Ala His
1 5 10 15

Lys Pro Pro Gly Gly Gly Ser Phe Arg Thr Pro Ile Gln Glu Glu Gln
20 25 30

Ala Asp Ala His Ser Thr Leu Ala Lys Ile
35 40

<210> SEQ ID NO 33
<211> LENGTH: 97
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic polypeptide"

<400> SEQUENCE: 33

Cys Ser Arg Ala Ala Arg Gly Thr Ile Gly Ala Arg Arg Thr Gly Gln
1 5 10 15

Pro Leu Lys Glu Asp Pro Ser Ala Val Pro Val Phe Ser Val Asp Tyr
20 25 30

Gly Glu Leu Asp Phe Gln Trp Arg Glu Lys Thr Pro Glu Pro Pro Val
35 40 45

Pro Cys Val Pro Glu Gln Thr Glu Tyr Ala Thr Ile Val Phe Pro Ser
50 55 60

Gly Met Gly Thr Ser Ser Pro Ala Arg Arg Gly Ser Ala Asp Gly Pro
65 70 75 80

Arg Ser Ala Gln Pro Leu Arg Pro Glu Asp Gly His Cys Ser Trp Pro
85 90 95

Leu

<210> SEQ ID NO 34
<211> LENGTH: 109
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic polypeptide"

<400> SEQUENCE: 34

Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
1 5 10 15

Asp Arg Val Thr Ile Thr Cys Lys Ala Ser Arg Asp Ile Arg Ser Tyr
20 25 30

Leu Thr Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Thr Leu Ile
35 40 45

Tyr Tyr Ala Thr Ser Leu Ala Asp Gly Val Pro Ser Arg Phe Ser Gly
50 55 60

Ser Gly Ser Gly Gln Asp Tyr Ser Leu Thr Ile Ser Ser Leu Glu Ser
65 70 75 80

Asp Asp Thr Ala Thr Tyr Tyr Cys Leu Gln His Gly Glu Ser Pro Phe
85 90 95

Thr Phe Gly Ser Gly Thr Lys Leu Glu Ile Lys Arg Ala
100 105

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<210> SEQ ID NO 35
<211> LENGTH: 119
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic polypeptide"

<400> SEQUENCE: 35

Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Lys Pro Gly Gly
1 5 10 15

Ser Leu Lys Leu Ser Cys Ala Ala Ser Gly Phe Lys Phe Ser Arg Tyr
20 25 30

Ala Met Ser Trp Val Arg Gln Ala Pro Gly Lys Arg Leu Glu Trp Val
35 40 45

Ala Thr Ile Ser Ser Gly Gly Ser Tyr Ile Tyr Tyr Pro Asp Ser Val
50 55 60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Val Lys Asn Thr Leu Tyr
65 70 75 80

Leu Gln Met Ser Ser Leu Arg Ser Glu Asp Thr Ala Met Tyr Tyr Cys
85 90 95

Ala Arg Arg Asp Tyr Asp Leu Asp Tyr Phe Asp Ser Trp Gly Gln Gly
100 105 110

Thr Leu Val Thr Val Ser Ser
115

<210> SEQ ID NO 36
<211> LENGTH: 18
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic peptide"

<400> SEQUENCE: 36

Gly Ser Thr Ser Gly Gly Gly Ser Gly Gly Gly Ser Gly Gly Gly Gly
1 5 10 15

Ser Ser

<210> SEQ ID NO 37
<211> LENGTH: 20
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic peptide"

<400> SEQUENCE: 37

Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly
1 5 10 15

Gly Gly Gly Ser
20

<210> SEQ ID NO 38
<211> LENGTH: 246
<212> TYPE: PRT

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<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic polypeptide"

<400> SEQUENCE: 38

Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Lys Pro Gly Gly
1 5 10 15

Ser Leu Lys Leu Ser Cys Ala Ala Ser Gly Phe Lys Phe Ser Arg Tyr
20 25 30

Ala Met Ser Trp Val Arg Gln Ala Pro Gly Lys Arg Leu Glu Trp Val
35 40 45

Ala Thr Ile Ser Ser Gly Gly Ser Tyr Ile Tyr Tyr Pro Asp Ser Val
50 55 60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Val Lys Asn Thr Leu Tyr
65 70 75 80

Leu Gln Met Ser Ser Leu Arg Ser Glu Asp Thr Ala Met Tyr Tyr Cys
85 90 95

Ala Arg Arg Asp Tyr Asp Leu Asp Tyr Phe Asp Ser Trp Gly Gln Gly
100 105 110

Thr Leu Val Thr Val Ser Ser Gly Ser Thr Ser Gly Gly Gly Ser Gly
115 120 125

Gly Gly Ser Gly Gly Gly Gly Ser Ser Asp Ile Gln Met Thr Gln Ser
130 135 140

Pro Ser Ser Leu Ser Ala Ser Val Gly Asp Arg Val Thr Ile Thr Cys
145 150 155 160

Lys Ala Ser Arg Asp Ile Arg Ser Tyr Leu Thr Trp Tyr Gln Gln Lys
165 170 175

Pro Gly Lys Ala Pro Lys Thr Leu Ile Tyr Tyr Ala Thr Ser Leu Ala
180 185 190

Asp Gly Val Pro Ser Arg Phe Ser Gly Ser Gly Ser Gly Gln Asp Tyr
195 200 205

Ser Leu Thr Ile Ser Ser Leu Glu Ser Asp Asp Thr Ala Thr Tyr Tyr
210 215 220

Cys Leu Gln His Gly Glu Ser Pro Phe Thr Phe Gly Ser Gly Thr Lys
225 230 235 240

Leu Glu Ile Lys Arg Ala
245

<210> SEQ ID NO 39
<211> LENGTH: 248
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic polypeptide"

<400> SEQUENCE: 39

Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Lys Pro Gly Gly
1 5 10 15

Ser Leu Lys Leu Ser Cys Ala Ala Ser Gly Phe Lys Phe Ser Arg Tyr
20 25 30

Ala Met Ser Trp Val Arg Gln Ala Pro Gly Lys Arg Leu Glu Trp Val
35 40 45

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Ala Thr Ile Ser Ser Gly Gly Ser Tyr Ile Tyr Tyr Pro Asp Ser Val
    50                  55                  60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Val Lys Asn Thr Leu Tyr
65                  70                  75                  80

Leu Gln Met Ser Ser Leu Arg Ser Glu Asp Thr Ala Met Tyr Tyr Cys
                85                  90                  95

Ala Arg Arg Asp Tyr Asp Leu Asp Tyr Phe Asp Ser Trp Gly Gln Gly
            100                 105                 110

Thr Leu Val Thr Val Ser Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly
        115                 120                 125

Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Asp Ile Gln Met Thr
    130                 135                 140

Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly Asp Arg Val Thr Ile
145                 150                 155                 160

Thr Cys Lys Ala Ser Arg Asp Ile Arg Ser Tyr Leu Thr Trp Tyr Gln
                165                 170                 175

Gln Lys Pro Gly Lys Ala Pro Lys Thr Leu Ile Tyr Tyr Ala Thr Ser
            180                 185                 190

Leu Ala Asp Gly Val Pro Ser Arg Phe Ser Gly Ser Gly Ser Gly Gln
        195                 200                 205

Asp Tyr Ser Leu Thr Ile Ser Ser Leu Glu Ser Asp Asp Thr Ala Thr
    210                 215                 220

Tyr Tyr Cys Leu Gln His Gly Glu Ser Pro Phe Thr Phe Gly Ser Gly
225                 230                 235                 240

Thr Lys Leu Glu Ile Lys Arg Ala
                245


<210> SEQ ID NO 40
<211> LENGTH: 246
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
      Synthetic polypeptide"

<400> SEQUENCE: 40

Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
1               5                   10                  15

Asp Arg Val Thr Ile Thr Cys Lys Ala Ser Arg Asp Ile Arg Ser Tyr
            20                  25                  30

Leu Thr Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Thr Leu Ile
        35                  40                  45

Tyr Tyr Ala Thr Ser Leu Ala Asp Gly Val Pro Ser Arg Phe Ser Gly
    50                  55                  60

Ser Gly Ser Gly Gln Asp Tyr Ser Leu Thr Ile Ser Ser Leu Glu Ser
65                  70                  75                  80

Asp Asp Thr Ala Thr Tyr Tyr Cys Leu Gln His Gly Glu Ser Pro Phe
                85                  90                  95

Thr Phe Gly Ser Gly Thr Lys Leu Glu Ile Lys Arg Ala Gly Ser Thr
            100                 105                 110

Ser Gly Gly Gly Ser Gly Gly Gly Ser Gly Gly Gly Gly Ser Ser Glu
        115                 120                 125
```

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```
Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Lys Pro Gly Gly Ser
    130                 135                 140

Leu Lys Leu Ser Cys Ala Ala Ser Gly Phe Lys Phe Ser Arg Tyr Ala
145                 150                 155                 160

Met Ser Trp Val Arg Gln Ala Pro Gly Lys Arg Leu Glu Trp Val Ala
                165                 170                 175

Thr Ile Ser Ser Gly Gly Ser Tyr Ile Tyr Tyr Pro Asp Ser Val Lys
            180                 185                 190

Gly Arg Phe Thr Ile Ser Arg Asp Asn Val Lys Asn Thr Leu Tyr Leu
        195                 200                 205

Gln Met Ser Ser Leu Arg Ser Glu Asp Thr Ala Met Tyr Tyr Cys Ala
    210                 215                 220

Arg Arg Asp Tyr Asp Leu Asp Tyr Phe Asp Ser Trp Gly Gln Gly Thr
225                 230                 235                 240

Leu Val Thr Val Ser Ser
                245


<210> SEQ ID NO 41
<211> LENGTH: 248
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
      Synthetic polypeptide"

<400> SEQUENCE: 41

Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
1               5                   10                  15

Asp Arg Val Thr Ile Thr Cys Lys Ala Ser Arg Asp Ile Arg Ser Tyr
            20                  25                  30

Leu Thr Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Thr Leu Ile
        35                  40                  45

Tyr Tyr Ala Thr Ser Leu Ala Asp Gly Val Pro Ser Arg Phe Ser Gly
    50                  55                  60

Ser Gly Ser Gly Gln Asp Tyr Ser Leu Thr Ile Ser Ser Leu Glu Ser
65                  70                  75                  80

Asp Asp Thr Ala Thr Tyr Tyr Cys Leu Gln His Gly Glu Ser Pro Phe
                85                  90                  95

Thr Phe Gly Ser Gly Thr Lys Leu Glu Ile Lys Arg Ala Gly Gly Gly
            100                 105                 110

Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly
        115                 120                 125

Ser Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Lys Pro Gly
    130                 135                 140

Gly Ser Leu Lys Leu Ser Cys Ala Ala Ser Gly Phe Lys Phe Ser Arg
145                 150                 155                 160

Tyr Ala Met Ser Trp Val Arg Gln Ala Pro Gly Lys Arg Leu Glu Trp
                165                 170                 175

Val Ala Thr Ile Ser Ser Gly Gly Ser Tyr Ile Tyr Tyr Pro Asp Ser
            180                 185                 190

Val Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Val Lys Asn Thr Leu
        195                 200                 205

Tyr Leu Gln Met Ser Ser Leu Arg Ser Glu Asp Thr Ala Met Tyr Tyr
```

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```
    210                 215                 220

Cys Ala Arg Arg Asp Tyr Asp Leu Asp Tyr Phe Asp Ser Trp Gly Gln
225                 230                 235                 240

Gly Thr Leu Val Thr Val Ser Ser
                245
```

<210> SEQ ID NO 42
<211> LENGTH: 738
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic polynucleotide"

<400> SEQUENCE: 42

```
gaagtccaat tggtcgagag cggaggtggg cttgttaaac caggaggcag tttaaaatta     60

tcatgtgctg cctcgggttt caagttctcg cggtatgcta tgtcctgggt acgccaagca    120

cctggaaagc gtttagaatg ggtggccaca attagtagtg gtggttcata tatatattat    180

cccgactccg tcaaaggaag gttcacgatt tcaagggaca atgtgaagaa caccctctac    240

ttacagatga gtagtctgcg ttctgaggat accgctatgt actactgtgc tcggagagat    300

tacgatctgg attatttcga cagctggggt cagggcacac tcgttacagt atcctcgggg    360

tcaacgtcgg gcgggggttc cggtggagga agtggaggtg gtggaagttc tgacatccaa    420

atgacacaaa gtcctagctc tctctcagca agtgttggcg accgtgtgac catcacatgt    480

aaagcttcaa gggatattcg cagctacctg acttggtacc aacaaaagcc cggaaaagcg    540

cctaaaacgc ttatttacta tgccaccagc ctcgcagatg gtgtcccctc cagattttct    600

ggatcgggat cagggcaaga ttatagtctt acgatatcga gtcttgagtc ggacgatact    660

gccacatact actgcttaca gcacggggaa agcccattca cattcggaag tggtacgaaa    720

ctcgagatca aacgggca                                                  738
```

<210> SEQ ID NO 43
<211> LENGTH: 744
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic polynucleotide"

<400> SEQUENCE: 43

```
gaagtccaat tggtcgagag cggaggtggg cttgttaaac caggaggcag tttaaaatta     60

tcatgtgctg cctcgggttt caagttctcg cggtatgcta tgtcctgggt acgccaagca    120

cctggaaagc gtttagaatg ggtggccaca attagtagtg gtggttcata tatatattat    180

cccgactccg tcaaaggaag gttcacgatt tcaagggaca atgtgaagaa caccctctac    240

ttacagatga gtagtctgcg ttctgaggat accgctatgt actactgtgc tcggagagat    300

tacgatctgg attatttcga cagctggggt cagggcacac tcgttacagt atcctcgggc    360

ggcggcggaa gtggcggcgg cggctcaggc gggggggggtt ctgggggcgg cggttcagac    420

atccaaatga cacaaagtcc tagctctctc tcagcaagtg ttggcgaccg tgtgaccatc    480

acatgtaaag cttcaaggga tattcgcagc tacctgactt ggtaccaaca aaagcccgga    540
```

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aaagcgccta aaacgcttat ttactatgcc accagcctcg cagatggtgt cccctccaga 600

ttttctggat cgggatcagg gcaagattat agtcttacga tatcgagtct tgagtcggac 660

gatactgcca catactactg cttacagcac ggggaaagcc cattcacatt cggaagtggt 720

acgaaactcg agatcaaacg ggca 744

<210> SEQ ID NO 44
<211> LENGTH: 738
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 44

gacatccaaa tgacacaaag tcctagctct ctctcagcaa gtgttggcga ccgtgtgacc 60

atcacatgta aagcttcaag ggatattcgc agctacctga cttggtacca acaaaagccc 120

ggaaaagcgc ctaaaacgct tatttactat gccaccagcc tcgcagatgg tgtcccctcc 180

agattttctg gatcgggatc agggcaagat tatagtctta cgatatcgag tcttgagtcg 240

gacgatactg ccacatacta ctgcttacag cacggggaaa gcccattcac attcggaagt 300

ggtacgaaac tcgagatcaa acgggcaggg tcaacgtcgg gcgggggttc cggtggagga 360

agtggaggtg gtggaagttc tgaagtccaa ttggtcgaga gcggaggtgg gcttgttaaa 420

ccaggaggca gtttaaaatt atcatgtgct gcctcgggtt tcaagttctc gcggtatgct 480

atgtcctggg tacgccaagc acctggaaag cgtttagaat gggtggccac aattagtagt 540

ggtggttcat atatatatta tcccgactcc gtcaaaggaa ggttcacgat ttcaagggac 600

aatgtgaaga acaccctcta cttacagatg agtagtctgc gttctgagga taccgctatg 660

tactactgtg ctcggagaga ttacgatctg gattatttcg acagctgggg tcagggcaca 720

ctcgttacag tatcctcg 738

<210> SEQ ID NO 45
<211> LENGTH: 744
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 45

gacatccaaa tgacacaaag tcctagctct ctctcagcaa gtgttggcga ccgtgtgacc 60

atcacatgta aagcttcaag ggatattcgc agctacctga cttggtacca acaaaagccc 120

ggaaaagcgc ctaaaacgct tatttactat gccaccagcc tcgcagatgg tgtcccctcc 180

agattttctg gatcgggatc agggcaagat tatagtctta cgatatcgag tcttgagtcg 240

gacgatactg ccacatacta ctgcttacag cacggggaaa gcccattcac attcggaagt 300

ggtacgaaac tcgagatcaa acgggcaggc ggcggcggaa gtggcggcgg cggctcaggc 360

gggggggggtt ctgggggcgg cggttcagaa gtccaattgg tcgagagcgg aggtgggctt 420

gttaaaccag gaggcagttt aaaattatca tgtgctgcct cgggtttcaa gttctcgcgg 480

tatgctatgt cctgggtacg ccaagcacct ggaaagcgtt tagaatgggt ggccacaatt 540

agtagtggtg gttcatatat atattatccc gactccgtca aaggaaggtt cacgatttca 600

agggacaatg tgaagaacac cctctactta cagatgagta gtctgcgttc tgaggatacc 660

gctatgtact actgtgctcg gagagattac gatctggatt atttcgacag ctggggtcag 720

ggcacactcg ttacagtatc ctcg 744

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<210> SEQ ID NO 46
<211> LENGTH: 235
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 46

Met Ala Leu Pro Val Thr Ala Leu Leu Leu Pro Leu Ala Leu Leu Leu
1 5 10 15

His Ala Ala Arg Pro Ser Gln Phe Arg Val Ser Pro Leu Asp Arg Thr
20 25 30

Trp Asn Leu Gly Glu Thr Val Glu Leu Lys Cys Gln Val Leu Leu Ser
35 40 45

Asn Pro Thr Ser Gly Cys Ser Trp Leu Phe Gln Pro Arg Gly Ala Ala
50 55 60

Ala Ser Pro Thr Phe Leu Leu Tyr Leu Ser Gln Asn Lys Pro Lys Ala
65 70 75 80

Ala Glu Gly Leu Asp Thr Gln Arg Phe Ser Gly Lys Arg Leu Gly Asp
85 90 95

Thr Phe Val Leu Thr Leu Ser Asp Phe Arg Arg Glu Asn Glu Gly Tyr
100 105 110

Tyr Phe Cys Ser Ala Leu Ser Asn Ser Ile Met Tyr Phe Ser His Phe
115 120 125

Val Pro Val Phe Leu Pro Ala Lys Pro Thr Thr Thr Pro Ala Pro Arg
130 135 140

Pro Pro Thr Pro Ala Pro Thr Ile Ala Ser Gln Pro Leu Ser Leu Arg
145 150 155 160

Pro Glu Ala Cys Arg Pro Ala Ala Gly Gly Ala Val His Thr Arg Gly
165 170 175

Leu Asp Phe Ala Cys Asp Ile Tyr Ile Trp Ala Pro Leu Ala Gly Thr
180 185 190

Cys Gly Val Leu Leu Leu Ser Leu Val Ile Thr Leu Tyr Cys Asn His
195 200 205

Arg Asn Arg Arg Arg Val Cys Lys Cys Pro Arg Pro Val Val Lys Ser
210 215 220

Gly Asp Lys Pro Ser Leu Ser Ala Arg Tyr Val
225 230 235

<210> SEQ ID NO 47
<211> LENGTH: 198
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 47

Met Ala Leu Pro Val Thr Ala Leu Leu Leu Pro Leu Ala Leu Leu Leu
1 5 10 15

His Ala Ala Arg Pro Ser Gln Phe Arg Val Ser Pro Leu Asp Arg Thr
20 25 30

Trp Asn Leu Gly Glu Thr Val Glu Leu Lys Cys Gln Val Leu Leu Ser
35 40 45

Asn Pro Thr Ser Gly Cys Ser Trp Leu Phe Gln Pro Arg Gly Ala Ala
50 55 60

Ala Ser Pro Thr Phe Leu Leu Tyr Leu Ser Gln Asn Lys Pro Lys Ala
65 70 75 80

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Ala Glu Gly Leu Asp Thr Gln Arg Phe Ser Gly Lys Arg Leu Gly Asp
                85                  90                  95

Thr Phe Val Leu Thr Leu Ser Asp Phe Arg Arg Glu Asn Glu Gly Tyr
            100                 105                 110

Tyr Phe Cys Ser Ala Leu Ser Asn Ser Ile Met Tyr Phe Ser His Phe
        115                 120                 125

Val Pro Val Phe Leu Pro Ala Lys Pro Thr Thr Thr Pro Ala Pro Arg
    130                 135                 140

Pro Pro Thr Pro Ala Pro Thr Ile Ala Ser Gln Pro Leu Ser Leu Arg
145                 150                 155                 160

Pro Glu Ala Cys Arg Pro Ala Ala Gly Gly Ala Gly Asn Arg Arg Arg
                165                 170                 175

Val Cys Lys Cys Pro Arg Pro Val Val Lys Ser Gly Asp Lys Pro Ser
            180                 185                 190

Leu Ser Ala Arg Tyr Val
        195


<210> SEQ ID NO 48
<211> LENGTH: 235
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 48

Met Ala Leu Pro Val Thr Ala Leu Leu Leu Pro Leu Ala Leu Leu Leu
1               5                   10                  15

His Ala Ala Arg Pro Ser Gln Phe Arg Val Ser Pro Leu Asp Arg Thr
            20                  25                  30

Trp Asn Leu Gly Glu Thr Val Glu Leu Lys Cys Gln Val Leu Leu Ser
        35                  40                  45

Asn Pro Thr Ser Gly Cys Ser Trp Leu Phe Gln Pro Arg Gly Ala Ala
    50                  55                  60

Ala Ser Pro Thr Phe Leu Leu Tyr Leu Ser Gln Asn Lys Pro Lys Ala
65                  70                  75                  80

Ala Glu Gly Leu Asp Thr Gln Arg Phe Ser Gly Lys Arg Leu Gly Asp
                85                  90                  95

Thr Phe Val Leu Thr Leu Ser Asp Phe Arg Arg Glu Asn Glu Gly Tyr
            100                 105                 110

Tyr Phe Cys Ser Ala Leu Ser Asn Ser Ile Met Tyr Phe Ser His Phe
        115                 120                 125

Val Pro Val Phe Leu Pro Ala Lys Pro Thr Thr Thr Pro Ala Pro Arg
    130                 135                 140

Pro Pro Thr Pro Ala Pro Thr Ile Ala Ser Gln Pro Leu Ser Leu Arg
145                 150                 155                 160

Pro Glu Ala Cys Arg Pro Ala Ala Gly Gly Ala Val His Thr Arg Gly
                165                 170                 175

Leu Asp Phe Ala Cys Asp Ile Tyr Ile Trp Ala Pro Leu Ala Gly Thr
            180                 185                 190

Cys Gly Val Leu Leu Leu Ser Leu Val Ile Thr Leu Tyr Cys Asn His
        195                 200                 205

Arg Asn Arg Arg Arg Val Cys Lys Cys Pro Arg Pro Val Val Lys Ser
    210                 215                 220

Gly Asp Lys Pro Ser Leu Ser Ala Arg Tyr Val
225                 230                 235
```

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<210> SEQ ID NO 49
<211> LENGTH: 246
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 49

Met Arg Pro Arg Leu Trp Leu Leu Leu Ala Ala Gln Leu Thr Val Leu
1 5 10 15

His Gly Asn Ser Val Leu Gln Gln Thr Pro Ala Tyr Ile Lys Val Gln
20 25 30

Thr Asn Lys Met Val Met Leu Ser Cys Glu Ala Lys Ile Ser Leu Ser
35 40 45

Asn Met Arg Ile Tyr Trp Leu Arg Gln Arg Gln Ala Pro Ser Ser Asp
50 55 60

Ser His His Glu Phe Leu Ala Leu Trp Asp Ser Ala Lys Gly Thr Ile
65 70 75 80

His Gly Glu Glu Val Glu Gln Glu Lys Ile Ala Val Phe Arg Asp Ala
85 90 95

Ser Arg Phe Ile Leu Asn Leu Thr Ser Val Lys Pro Glu Asp Ser Gly
100 105 110

Ile Tyr Phe Cys Met Ile Val Gly Ser Pro Glu Leu Thr Phe Gly Lys
115 120 125

Gly Thr Gln Leu Ser Val Val Asp Phe Leu Pro Thr Thr Ala Gln Pro
130 135 140

Thr Lys Lys Ser Thr Leu Lys Lys Arg Val Cys Arg Leu Pro Arg Pro
145 150 155 160

Glu Thr Gln Lys Gly Pro Leu Cys Ser Pro Ile Thr Leu Gly Leu Leu
165 170 175

Val Ala Gly Val Leu Val Leu Leu Val Ser Leu Gly Val Ala Ile His
180 185 190

Leu Cys Cys Arg Arg Arg Arg Ala Arg Leu Arg Phe Met Lys Gln Lys
195 200 205

Phe Asn Ile Val Cys Leu Lys Ile Ser Gly Phe Thr Thr Cys Cys Cys
210 215 220

Phe Gln Ile Leu Gln Met Ser Arg Glu Tyr Gly Phe Gly Val Leu Leu
225 230 235 240

Gln Lys Asp Ile Gly Gln
245

<210> SEQ ID NO 50
<211> LENGTH: 198
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 50

Met Arg Pro Arg Leu Trp Leu Leu Leu Ala Ala Gln Leu Thr Val Leu
1 5 10 15

His Gly Asn Ser Val Leu Gln Gln Thr Pro Ala Tyr Ile Lys Val Gln
20 25 30

Thr Asn Lys Met Val Met Leu Ser Cys Glu Ala Lys Ile Ser Leu Ser
35 40 45

Asn Met Arg Ile Tyr Trp Leu Arg Gln Arg Gln Ala Pro Ser Ser Asp
50 55 60

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Ser His His Glu Phe Leu Ala Leu Trp Asp Ser Ala Lys Gly Thr Ile
65                  70                  75                  80

His Gly Glu Glu Val Glu Gln Glu Lys Ile Ala Val Phe Arg Asp Ala
                85                  90                  95

Ser Arg Phe Ile Leu Asn Leu Thr Ser Val Lys Pro Glu Asp Ser Gly
            100                 105                 110

Ile Tyr Phe Cys Met Ile Val Gly Ser Pro Glu Leu Thr Phe Gly Lys
        115                 120                 125

Gly Thr Gln Leu Ser Val Val Asp Phe Leu Pro Thr Thr Ala Gln Pro
    130                 135                 140

Thr Lys Lys Ser Thr Leu Lys Lys Arg Val Cys Arg Leu Pro Arg Pro
145                 150                 155                 160

Glu Thr Gln Lys Gly Leu Lys Gly Lys Val Tyr Gln Glu Pro Leu Ser
                165                 170                 175

Pro Asn Ala Cys Met Asp Thr Thr Ala Ile Leu Gln Pro His Arg Ser
            180                 185                 190

Cys Leu Thr His Gly Ser
        195


<210> SEQ ID NO 51
<211> LENGTH: 243
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 51

Met Arg Pro Arg Leu Trp Leu Leu Leu Ala Ala Gln Leu Thr Val Leu
1               5                   10                  15

His Gly Asn Ser Val Leu Gln Gln Thr Pro Ala Tyr Ile Lys Val Gln
            20                  25                  30

Thr Asn Lys Met Val Met Leu Ser Cys Glu Ala Lys Ile Ser Leu Ser
        35                  40                  45

Asn Met Arg Ile Tyr Trp Leu Arg Gln Arg Gln Ala Pro Ser Ser Asp
    50                  55                  60

Ser His His Glu Phe Leu Ala Leu Trp Asp Ser Ala Lys Gly Thr Ile
65                  70                  75                  80

His Gly Glu Glu Val Glu Gln Glu Lys Ile Ala Val Phe Arg Asp Ala
                85                  90                  95

Ser Arg Phe Ile Leu Asn Leu Thr Ser Val Lys Pro Glu Asp Ser Gly
            100                 105                 110

Ile Tyr Phe Cys Met Ile Val Gly Ser Pro Glu Leu Thr Phe Gly Lys
        115                 120                 125

Gly Thr Gln Leu Ser Val Val Asp Phe Leu Pro Thr Thr Ala Gln Pro
    130                 135                 140

Thr Lys Lys Ser Thr Leu Lys Lys Arg Val Cys Arg Leu Pro Arg Pro
145                 150                 155                 160

Glu Thr Gln Lys Gly Pro Leu Cys Ser Pro Ile Thr Leu Gly Leu Leu
                165                 170                 175

Val Ala Gly Val Leu Val Leu Leu Val Ser Leu Gly Val Ala Ile His
            180                 185                 190

Leu Cys Cys Arg Arg Arg Arg Ala Arg Leu Arg Phe Met Lys Gln Pro
        195                 200                 205

Gln Gly Glu Gly Ile Ser Gly Thr Phe Val Pro Gln Cys Leu His Gly
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    210                 215                 220

Tyr Tyr Ser Asn Thr Thr Thr Ser Gln Lys Leu Leu Asn Pro Trp Ile
225                 230                 235                 240

Leu Lys Thr


<210> SEQ ID NO 52
<211> LENGTH: 213
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 52

Met Arg Pro Arg Leu Trp Leu Leu Leu Ala Ala Gln Leu Thr Val Leu
1               5                   10                  15

His Gly Asn Ser Val Leu Gln Gln Thr Pro Ala Tyr Ile Lys Val Gln
            20                  25                  30

Thr Asn Lys Met Val Met Leu Ser Cys Glu Ala Lys Ile Ser Leu Ser
        35                  40                  45

Asn Met Arg Ile Tyr Trp Leu Arg Gln Arg Gln Ala Pro Ser Ser Asp
    50                  55                  60

Ser His His Glu Phe Leu Ala Leu Trp Asp Ser Ala Lys Gly Thr Ile
65                  70                  75                  80

His Gly Glu Glu Val Glu Gln Glu Lys Ile Ala Val Phe Arg Asp Ala
                85                  90                  95

Ser Arg Phe Ile Leu Asn Leu Thr Ser Val Lys Pro Glu Asp Ser Gly
            100                 105                 110

Ile Tyr Phe Cys Met Ile Val Gly Ser Pro Glu Leu Thr Phe Gly Lys
        115                 120                 125

Gly Thr Gln Leu Ser Val Val Asp Phe Leu Pro Thr Thr Ala Gln Pro
    130                 135                 140

Thr Lys Lys Ser Thr Leu Lys Lys Arg Val Cys Arg Leu Pro Arg Pro
145                 150                 155                 160

Glu Thr Gln Lys Gly Arg Arg Arg Arg Ala Arg Leu Arg Phe Met Lys
                165                 170                 175

Gln Pro Gln Gly Glu Gly Ile Ser Gly Thr Phe Val Pro Gln Cys Leu
            180                 185                 190

His Gly Tyr Tyr Ser Asn Thr Thr Thr Ser Gln Lys Leu Leu Asn Pro
        195                 200                 205

Trp Ile Leu Lys Thr
    210


<210> SEQ ID NO 53
<211> LENGTH: 221
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 53

Met Arg Pro Arg Leu Trp Leu Leu Leu Ala Ala Gln Leu Thr Val Leu
1               5                   10                  15

His Gly Asn Ser Val Leu Gln Gln Thr Pro Ala Tyr Ile Lys Val Gln
            20                  25                  30

Thr Asn Lys Met Val Met Leu Ser Cys Glu Ala Lys Ile Ser Leu Ser
        35                  40                  45

Asn Met Arg Ile Tyr Trp Leu Arg Gln Arg Gln Ala Pro Ser Ser Asp
    50                  55                  60
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```
Ser His His Glu Phe Leu Ala Leu Trp Asp Ser Ala Lys Gly Thr Ile
65                  70                  75                  80

His Gly Glu Glu Val Glu Gln Glu Lys Ile Ala Val Phe Arg Asp Ala
                85                  90                  95

Ser Arg Phe Ile Leu Asn Leu Thr Ser Val Lys Pro Glu Asp Ser Gly
            100                 105                 110

Ile Tyr Phe Cys Met Ile Val Gly Ser Pro Glu Leu Thr Phe Gly Lys
        115                 120                 125

Gly Thr Gln Leu Ser Val Val Asp Phe Leu Pro Thr Thr Ala Gln Pro
    130                 135                 140

Thr Lys Lys Ser Thr Leu Lys Lys Arg Val Cys Arg Leu Pro Arg Pro
145                 150                 155                 160

Glu Thr Gln Lys Gly Pro Leu Cys Ser Pro Ile Thr Leu Gly Leu Leu
                165                 170                 175

Val Ala Gly Val Leu Val Leu Leu Val Ser Leu Gly Val Ala Ile His
            180                 185                 190

Leu Cys Cys Arg Arg Arg Arg Ala Arg Leu Arg Phe Met Lys Gln Leu
        195                 200                 205

Arg Leu His Pro Leu Glu Lys Cys Ser Arg Met Asp Tyr
    210                 215                 220


<210> SEQ ID NO 54
<211> LENGTH: 210
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 54

Met Arg Pro Arg Leu Trp Leu Leu Leu Ala Ala Gln Leu Thr Val Leu
1               5                   10                  15

His Gly Asn Ser Val Leu Gln Gln Thr Pro Ala Tyr Ile Lys Val Gln
            20                  25                  30

Thr Asn Lys Met Val Met Leu Ser Cys Glu Ala Lys Ile Ser Leu Ser
        35                  40                  45

Asn Met Arg Ile Tyr Trp Leu Arg Gln Arg Gln Ala Pro Ser Ser Asp
    50                  55                  60

Ser His His Glu Phe Leu Ala Leu Trp Asp Ser Ala Lys Gly Thr Ile
65                  70                  75                  80

His Gly Glu Glu Val Glu Gln Glu Lys Ile Ala Val Phe Arg Asp Ala
                85                  90                  95

Ser Arg Phe Ile Leu Asn Leu Thr Ser Val Lys Pro Glu Asp Ser Gly
            100                 105                 110

Ile Tyr Phe Cys Met Ile Val Gly Ser Pro Glu Leu Thr Phe Gly Lys
        115                 120                 125

Gly Thr Gln Leu Ser Val Val Asp Phe Leu Pro Thr Thr Ala Gln Pro
    130                 135                 140

Thr Lys Lys Ser Thr Leu Lys Lys Arg Val Cys Arg Leu Pro Arg Pro
145                 150                 155                 160

Glu Thr Gln Lys Gly Pro Leu Cys Ser Pro Ile Thr Leu Gly Leu Leu
                165                 170                 175

Val Ala Gly Val Leu Val Leu Leu Val Ser Leu Gly Val Ala Ile His
            180                 185                 190

Leu Cys Cys Arg Arg Arg Arg Ala Arg Leu Arg Phe Met Lys Gln Phe
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        195                 200                 205

Tyr Lys
    210


<210> SEQ ID NO 55
<211> LENGTH: 163
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 55

Met Lys Trp Lys Ala Leu Phe Thr Ala Ala Ile Leu Gln Ala Gln Leu
1               5                   10                  15

Pro Ile Thr Glu Ala Gln Ser Phe Gly Leu Leu Asp Pro Lys Leu Cys
            20                  25                  30

Tyr Leu Leu Asp Gly Ile Leu Phe Ile Tyr Gly Val Ile Leu Thr Ala
        35                  40                  45

Leu Phe Leu Arg Val Lys Phe Ser Arg Ser Ala Asp Ala Pro Ala Tyr
    50                  55                  60

Gln Gln Gly Gln Asn Gln Leu Tyr Asn Glu Leu Asn Leu Gly Arg Arg
65                  70                  75                  80

Glu Glu Tyr Asp Val Leu Asp Lys Arg Arg Gly Arg Asp Pro Glu Met
                85                  90                  95

Gly Gly Lys Pro Arg Arg Lys Asn Pro Gln Glu Gly Leu Tyr Asn Glu
            100                 105                 110

Leu Gln Lys Asp Lys Met Ala Glu Ala Tyr Ser Glu Ile Gly Met Lys
        115                 120                 125

Gly Glu Arg Arg Arg Gly Lys Gly His Asp Gly Leu Tyr Gln Gly Leu
    130                 135                 140

Ser Thr Ala Thr Lys Asp Thr Tyr Asp Ala Leu His Met Gln Ala Leu
145                 150                 155                 160

Pro Pro Arg


<210> SEQ ID NO 56
<211> LENGTH: 164
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 56

Met Lys Trp Lys Ala Leu Phe Thr Ala Ala Ile Leu Gln Ala Gln Leu
1               5                   10                  15

Pro Ile Thr Glu Ala Gln Ser Phe Gly Leu Leu Asp Pro Lys Leu Cys
            20                  25                  30

Tyr Leu Leu Asp Gly Ile Leu Phe Ile Tyr Gly Val Ile Leu Thr Ala
        35                  40                  45

Leu Phe Leu Arg Val Lys Phe Ser Arg Ser Ala Asp Ala Pro Ala Tyr
    50                  55                  60

Gln Gln Gly Gln Asn Gln Leu Tyr Asn Glu Leu Asn Leu Gly Arg Arg
65                  70                  75                  80

Glu Glu Tyr Asp Val Leu Asp Lys Arg Arg Gly Arg Asp Pro Glu Met
                85                  90                  95

Gly Gly Lys Pro Gln Arg Arg Lys Asn Pro Gln Glu Gly Leu Tyr Asn
            100                 105                 110

Glu Leu Gln Lys Asp Lys Met Ala Glu Ala Tyr Ser Glu Ile Gly Met
        115                 120                 125
```

-continued

```
Lys Gly Glu Arg Arg Arg Gly Lys Gly His Asp Gly Leu Tyr Gln Gly
    130                 135                 140

Leu Ser Thr Ala Thr Lys Asp Thr Tyr Asp Ala Leu His Met Gln Ala
145                 150                 155                 160

Leu Pro Pro Arg
```

<210> SEQ ID NO 57
<211> LENGTH: 123
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 57

```
Met Leu Arg Leu Leu Leu Ala Leu Asn Leu Phe Pro Ser Ile Gln Val
1               5                   10                  15

Thr Gly Asn Lys Ile Leu Val Lys Gln Ser Pro Met Leu Val Ala Tyr
            20                  25                  30

Asp Asn Ala Val Asn Leu Ser Trp Lys His Leu Cys Pro Ser Pro Leu
        35                  40                  45

Phe Pro Gly Pro Ser Lys Pro Phe Trp Val Leu Val Val Val Gly Gly
    50                  55                  60

Val Leu Ala Cys Tyr Ser Leu Leu Val Thr Val Ala Phe Ile Ile Phe
65                  70                  75                  80

Trp Val Arg Ser Lys Arg Ser Arg Leu Leu His Ser Asp Tyr Met Asn
                85                  90                  95

Met Thr Pro Arg Arg Pro Gly Pro Thr Arg Lys His Tyr Gln Pro Tyr
            100                 105                 110

Ala Pro Pro Arg Asp Phe Ala Ala Tyr Arg Ser
        115                 120
```

<210> SEQ ID NO 58
<211> LENGTH: 101
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 58

```
Met Leu Arg Leu Leu Leu Ala Leu Asn Leu Phe Pro Ser Ile Gln Val
1               5                   10                  15

Thr Gly Lys His Leu Cys Pro Ser Pro Leu Phe Pro Gly Pro Ser Lys
            20                  25                  30

Pro Phe Trp Val Leu Val Val Val Gly Gly Val Leu Ala Cys Tyr Ser
        35                  40                  45

Leu Leu Val Thr Val Ala Phe Ile Ile Phe Trp Val Arg Ser Lys Arg
    50                  55                  60

Ser Arg Leu Leu His Ser Asp Tyr Met Asn Met Thr Pro Arg Arg Pro
65                  70                  75                  80

Gly Pro Thr Arg Lys His Tyr Gln Pro Tyr Ala Pro Pro Arg Asp Phe
                85                  90                  95

Ala Ala Tyr Arg Ser
            100
```

<210> SEQ ID NO 59
<211> LENGTH: 220
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

-continued

<400> SEQUENCE: 59

Met Leu Arg Leu Leu Leu Ala Leu Asn Leu Phe Pro Ser Ile Gln Val
1 5 10 15

Thr Gly Asn Lys Ile Leu Val Lys Gln Ser Pro Met Leu Val Ala Tyr
20 25 30

Asp Asn Ala Val Asn Leu Ser Cys Lys Tyr Ser Tyr Asn Leu Phe Ser
35 40 45

Arg Glu Phe Arg Ala Ser Leu His Lys Gly Leu Asp Ser Ala Val Glu
50 55 60

Val Cys Val Val Tyr Gly Asn Tyr Ser Gln Gln Leu Gln Val Tyr Ser
65 70 75 80

Lys Thr Gly Phe Asn Cys Asp Gly Lys Leu Gly Asn Glu Ser Val Thr
85 90 95

Phe Tyr Leu Gln Asn Leu Tyr Val Asn Gln Thr Asp Ile Tyr Phe Cys
100 105 110

Lys Ile Glu Val Met Tyr Pro Pro Pro Tyr Leu Asp Asn Glu Lys Ser
115 120 125

Asn Gly Thr Ile Ile His Val Lys Gly Lys His Leu Cys Pro Ser Pro
130 135 140

Leu Phe Pro Gly Pro Ser Lys Pro Phe Trp Val Leu Val Val Val Gly
145 150 155 160

Gly Val Leu Ala Cys Tyr Ser Leu Leu Val Thr Val Ala Phe Ile Ile
165 170 175

Phe Trp Val Arg Ser Lys Arg Ser Arg Leu Leu His Ser Asp Tyr Met
180 185 190

Asn Met Thr Pro Arg Arg Pro Gly Pro Thr Arg Lys His Tyr Gln Pro
195 200 205

Tyr Ala Pro Pro Arg Asp Phe Ala Ala Tyr Arg Ser
210 215 220

<210> SEQ ID NO 60
<211> LENGTH: 277
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 60

Met Cys Val Gly Ala Arg Arg Leu Gly Arg Gly Pro Cys Ala Ala Leu
1 5 10 15

Leu Leu Leu Gly Leu Gly Leu Ser Thr Val Thr Gly Leu His Cys Val
20 25 30

Gly Asp Thr Tyr Pro Ser Asn Asp Arg Cys Cys His Glu Cys Arg Pro
35 40 45

Gly Asn Gly Met Val Ser Arg Cys Ser Arg Ser Gln Asn Thr Val Cys
50 55 60

Arg Pro Cys Gly Pro Gly Phe Tyr Asn Asp Val Val Ser Ser Lys Pro
65 70 75 80

Cys Lys Pro Cys Thr Trp Cys Asn Leu Arg Ser Gly Ser Glu Arg Lys
85 90 95

Gln Leu Cys Thr Ala Thr Gln Asp Thr Val Cys Arg Cys Arg Ala Gly
100 105 110

Thr Gln Pro Leu Asp Ser Tyr Lys Pro Gly Val Asp Cys Ala Pro Cys
115 120 125

-continued

```
Pro Pro Gly His Phe Ser Pro Gly Asp Asn Gln Ala Cys Lys Pro Trp
    130                 135                 140

Thr Asn Cys Thr Leu Ala Gly Lys His Thr Leu Gln Pro Ala Ser Asn
145                 150                 155                 160

Ser Ser Asp Ala Ile Cys Glu Asp Arg Asp Pro Pro Ala Thr Gln Pro
                165                 170                 175

Gln Glu Thr Gln Gly Pro Pro Ala Arg Pro Ile Thr Val Gln Pro Thr
            180                 185                 190

Glu Ala Trp Pro Arg Thr Ser Gln Gly Pro Ser Thr Arg Pro Val Glu
        195                 200                 205

Val Pro Gly Gly Arg Ala Val Ala Ala Ile Leu Gly Leu Gly Leu Val
    210                 215                 220

Leu Gly Leu Leu Gly Pro Leu Ala Ile Leu Leu Ala Leu Tyr Leu Leu
225                 230                 235                 240

Arg Arg Asp Gln Arg Leu Pro Pro Asp Ala His Lys Pro Pro Gly Gly
                245                 250                 255

Gly Ser Phe Arg Thr Pro Ile Gln Glu Glu Gln Ala Asp Ala His Ser
            260                 265                 270

Thr Leu Ala Lys Ile
        275


<210> SEQ ID NO 61
<211> LENGTH: 174
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 61

Met Ala Cys Leu Gly Phe Gln Arg His Lys Ala Gln Leu Asn Leu Ala
1               5                   10                  15

Thr Arg Thr Trp Pro Cys Thr Leu Leu Phe Phe Leu Leu Phe Ile Pro
            20                  25                  30

Val Phe Cys Lys Ala Met His Val Ala Gln Pro Ala Val Val Leu Ala
        35                  40                  45

Ser Ser Arg Gly Ile Ala Ser Phe Val Cys Glu Tyr Ala Ser Pro Gly
    50                  55                  60

Lys Ala Thr Glu Val Arg Val Thr Val Leu Arg Gln Ala Asp Ser Gln
65                  70                  75                  80

Val Thr Glu Val Cys Ala Ala Thr Tyr Met Met Gly Asn Glu Leu Thr
                85                  90                  95

Phe Leu Asp Asp Ser Ile Cys Thr Gly Thr Ser Ser Gly Asn Gln Val
            100                 105                 110

Asn Leu Thr Ile Gln Gly Leu Arg Ala Met Asp Thr Gly Leu Tyr Ile
        115                 120                 125

Cys Lys Val Glu Leu Met Tyr Pro Pro Pro Tyr Tyr Leu Gly Ile Gly
    130                 135                 140

Asn Gly Thr Gln Ile Tyr Val Ile Ala Lys Glu Lys Lys Pro Ser Tyr
145                 150                 155                 160

Asn Arg Gly Leu Cys Glu Asn Ala Pro Asn Arg Ala Arg Met
                165                 170


<210> SEQ ID NO 62
<211> LENGTH: 223
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens
```

-continued

<400> SEQUENCE: 62

Met Ala Cys Leu Gly Phe Gln Arg His Lys Ala Gln Leu Asn Leu Ala
1 5 10 15

Thr Arg Thr Trp Pro Cys Thr Leu Leu Phe Phe Leu Leu Phe Ile Pro
20 25 30

Val Phe Cys Lys Ala Met His Val Ala Gln Pro Ala Val Val Leu Ala
35 40 45

Ser Ser Arg Gly Ile Ala Ser Phe Val Cys Glu Tyr Ala Ser Pro Gly
50 55 60

Lys Ala Thr Glu Val Arg Val Thr Val Leu Arg Gln Ala Asp Ser Gln
65 70 75 80

Val Thr Glu Val Cys Ala Ala Thr Tyr Met Met Gly Asn Glu Leu Thr
85 90 95

Phe Leu Asp Asp Ser Ile Cys Thr Gly Thr Ser Ser Gly Asn Gln Val
100 105 110

Asn Leu Thr Ile Gln Gly Leu Arg Ala Met Asp Thr Gly Leu Tyr Ile
115 120 125

Cys Lys Val Glu Leu Met Tyr Pro Pro Pro Tyr Tyr Leu Gly Ile Gly
130 135 140

Asn Gly Thr Gln Ile Tyr Val Ile Asp Pro Glu Pro Cys Pro Asp Ser
145 150 155 160

Asp Phe Leu Leu Trp Ile Leu Ala Ala Val Ser Ser Gly Leu Phe Phe
165 170 175

Tyr Ser Phe Leu Leu Thr Ala Val Ser Leu Ser Lys Met Leu Lys Lys
180 185 190

Arg Ser Pro Leu Thr Thr Gly Val Tyr Val Lys Met Pro Pro Thr Glu
195 200 205

Pro Glu Cys Glu Lys Gln Phe Gln Pro Tyr Phe Ile Pro Ile Asn
210 215 220

<210> SEQ ID NO 63
<211> LENGTH: 288
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 63

Met Gln Ile Pro Gln Ala Pro Trp Pro Val Val Trp Ala Val Leu Gln
1 5 10 15

Leu Gly Trp Arg Pro Gly Trp Phe Leu Asp Ser Pro Asp Arg Pro Trp
20 25 30

Asn Pro Pro Thr Phe Ser Pro Ala Leu Leu Val Val Thr Glu Gly Asp
35 40 45

Asn Ala Thr Phe Thr Cys Ser Phe Ser Asn Thr Ser Glu Ser Phe Val
50 55 60

Leu Asn Trp Tyr Arg Met Ser Pro Ser Asn Gln Thr Asp Lys Leu Ala
65 70 75 80

Ala Phe Pro Glu Asp Arg Ser Gln Pro Gly Gln Asp Cys Arg Phe Arg
85 90 95

Val Thr Gln Leu Pro Asn Gly Arg Asp Phe His Met Ser Val Val Arg
100 105 110

Ala Arg Arg Asn Asp Ser Gly Thr Tyr Leu Cys Gly Ala Ile Ser Leu
115 120 125

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```
Ala Pro Lys Ala Gln Ile Lys Glu Ser Leu Arg Ala Glu Leu Arg Val
    130                 135                 140

Thr Glu Arg Arg Ala Glu Val Pro Thr Ala His Pro Ser Pro Ser Pro
145                 150                 155                 160

Arg Pro Ala Gly Gln Phe Gln Thr Leu Val Val Gly Val Val Gly Gly
                165                 170                 175

Leu Leu Gly Ser Leu Val Leu Leu Val Trp Val Leu Ala Val Ile Cys
            180                 185                 190

Ser Arg Ala Ala Arg Gly Thr Ile Gly Ala Arg Arg Thr Gly Gln Pro
        195                 200                 205

Leu Lys Glu Asp Pro Ser Ala Val Pro Val Phe Ser Val Asp Tyr Gly
    210                 215                 220

Glu Leu Asp Phe Gln Trp Arg Glu Lys Thr Pro Glu Pro Pro Val Pro
225                 230                 235                 240

Cys Val Pro Glu Gln Thr Glu Tyr Ala Thr Ile Val Phe Pro Ser Gly
                245                 250                 255

Met Gly Thr Ser Ser Pro Ala Arg Arg Gly Ser Ala Asp Gly Pro Arg
            260                 265                 270

Ser Ala Gln Pro Leu Arg Pro Glu Asp Gly His Cys Ser Trp Pro Leu
        275                 280                 285


<210> SEQ ID NO 64
<211> LENGTH: 241
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 64

Met Ala Gln His Gly Ala Met Gly Ala Phe Arg Ala Leu Cys Gly Leu
1               5                   10                  15

Ala Leu Leu Cys Ala Leu Ser Leu Gly Gln Arg Pro Thr Gly Gly Pro
            20                  25                  30

Gly Cys Gly Pro Gly Arg Leu Leu Leu Gly Thr Gly Thr Asp Ala Arg
        35                  40                  45

Cys Cys Arg Val His Thr Thr Arg Cys Cys Arg Asp Tyr Pro Gly Glu
    50                  55                  60

Glu Cys Cys Ser Glu Trp Asp Cys Met Cys Val Gln Pro Glu Phe His
65                  70                  75                  80

Cys Gly Asp Pro Cys Cys Thr Thr Cys Arg His His Pro Cys Pro Pro
                85                  90                  95

Gly Gln Gly Val Gln Ser Gln Gly Lys Phe Ser Phe Gly Phe Gln Cys
            100                 105                 110

Ile Asp Cys Ala Ser Gly Thr Phe Ser Gly Gly His Glu Gly His Cys
        115                 120                 125

Lys Pro Trp Thr Asp Cys Thr Gln Phe Gly Phe Leu Thr Val Phe Pro
    130                 135                 140

Gly Asn Lys Thr His Asn Ala Val Cys Val Pro Gly Ser Pro Pro Ala
145                 150                 155                 160

Glu Pro Leu Gly Trp Leu Thr Val Val Leu Leu Ala Val Ala Ala Cys
                165                 170                 175

Val Leu Leu Leu Thr Ser Ala Gln Leu Gly Leu His Ile Trp Gln Leu
            180                 185                 190

Arg Ser Gln Cys Met Trp Pro Arg Glu Thr Gln Leu Leu Leu Glu Val
```

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```
        195                 200                 205

Pro Pro Ser Thr Glu Asp Ala Arg Ser Cys Gln Phe Pro Glu Glu Glu
    210                 215                 220

Arg Gly Glu Arg Ser Ala Glu Glu Lys Gly Arg Leu Gly Asp Leu Trp
225                 230                 235                 240

Val
```

<210> SEQ ID NO 65
<211> LENGTH: 255
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 65

```
Met Ala Gln His Gly Ala Met Gly Ala Phe Arg Ala Leu Cys Gly Leu
1               5                   10                  15

Ala Leu Leu Cys Ala Leu Ser Leu Gly Gln Arg Pro Thr Gly Gly Pro
            20                  25                  30

Gly Cys Gly Pro Gly Arg Leu Leu Leu Gly Thr Gly Thr Asp Ala Arg
        35                  40                  45

Cys Cys Arg Val His Thr Thr Arg Cys Cys Arg Asp Tyr Pro Gly Glu
    50                  55                  60

Glu Cys Cys Ser Glu Trp Asp Cys Met Cys Val Gln Pro Glu Phe His
65                  70                  75                  80

Cys Gly Asp Pro Cys Cys Thr Thr Cys Arg His His Pro Cys Pro Pro
                85                  90                  95

Gly Gln Gly Val Gln Ser Gln Gly Lys Phe Ser Phe Gly Phe Gln Cys
            100                 105                 110

Ile Asp Cys Ala Ser Gly Thr Phe Ser Gly Gly His Glu Gly His Cys
        115                 120                 125

Lys Pro Trp Thr Asp Cys Cys Trp Arg Cys Arg Arg Arg Pro Lys Thr
    130                 135                 140

Pro Glu Ala Ala Ser Ser Pro Arg Lys Ser Gly Ala Ser Asp Arg Gln
145                 150                 155                 160

Arg Arg Arg Gly Gly Trp Glu Thr Cys Gly Cys Glu Pro Gly Arg Pro
                165                 170                 175

Pro Gly Pro Pro Thr Ala Ala Ser Pro Ser Pro Gly Ala Pro Gln Ala
            180                 185                 190

Ala Gly Ala Leu Arg Ser Ala Leu Gly Arg Ala Leu Leu Pro Trp Gln
        195                 200                 205

Gln Lys Trp Val Gln Glu Gly Gly Ser Asp Gln Arg Pro Gly Pro Cys
    210                 215                 220

Ser Ser Ala Ala Ala Ala Gly Pro Cys Arg Arg Glu Arg Glu Thr Gln
225                 230                 235                 240

Ser Trp Pro Pro Ser Ser Leu Ala Gly Pro Asp Gly Val Gly Ser
                245                 250                 255
```

<210> SEQ ID NO 66
<211> LENGTH: 234
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 66

```
Met Ala Gln His Gly Ala Met Gly Ala Phe Arg Ala Leu Cys Gly Leu
1               5                   10                  15
```

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```
Ala Leu Leu Cys Ala Leu Ser Leu Gly Gln Arg Pro Thr Gly Gly Pro
            20                  25                  30

Gly Cys Gly Pro Gly Arg Leu Leu Leu Gly Thr Gly Thr Asp Ala Arg
        35                  40                  45

Cys Cys Arg Val His Thr Thr Arg Cys Cys Arg Asp Tyr Pro Gly Glu
    50                  55                  60

Glu Cys Cys Ser Glu Trp Asp Cys Met Cys Val Gln Pro Glu Phe His
65                  70                  75                  80

Cys Gly Asp Pro Cys Cys Thr Thr Cys Arg His His Pro Cys Pro Pro
                85                  90                  95

Gly Gln Gly Val Gln Ser Gln Gly Lys Phe Ser Phe Gly Phe Gln Cys
            100                 105                 110

Ile Asp Cys Ala Ser Gly Thr Phe Ser Gly Gly His Glu Gly His Cys
        115                 120                 125

Lys Pro Trp Thr Asp Cys Thr Gln Phe Gly Phe Leu Thr Val Phe Pro
    130                 135                 140

Gly Asn Lys Thr His Asn Ala Val Cys Val Pro Gly Ser Pro Pro Ala
145                 150                 155                 160

Glu Pro Leu Gly Trp Leu Thr Val Val Leu Leu Ala Val Ala Ala Cys
                165                 170                 175

Val Leu Leu Leu Thr Ser Ala Gln Leu Gly Leu His Ile Trp Gln Leu
            180                 185                 190

Arg Lys Thr Gln Leu Leu Leu Glu Val Pro Pro Ser Thr Glu Asp Ala
        195                 200                 205

Arg Ser Cys Gln Phe Pro Glu Glu Glu Arg Gly Glu Arg Ser Ala Glu
    210                 215                 220

Glu Lys Gly Arg Leu Gly Asp Leu Trp Val
225                 230


<210> SEQ ID NO 67
<211> LENGTH: 58
<212> TYPE: PRT
<213> ORGANISM: Unknown
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Unknown:
      GITR sequence"

<400> SEQUENCE: 67

Gln Leu Gly Leu His Ile Trp Gln Leu Arg Ser Gln Cys Met Trp Pro
1               5                   10                  15

Arg Glu Thr Gln Leu Leu Leu Glu Val Pro Pro Ser Thr Glu Asp Ala
            20                  25                  30

Arg Ser Cys Gln Phe Pro Glu Glu Glu Arg Gly Glu Arg Ser Ala Glu
        35                  40                  45

Glu Lys Gly Arg Leu Gly Asp Leu Trp Val
    50                  55


<210> SEQ ID NO 68
<211> LENGTH: 119
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
      Synthetic polypeptide"
```

-continued

<400> SEQUENCE: 68

Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Lys Pro Gly Gly
1 5 10 15

Ser Leu Lys Leu Ser Cys Ala Ala Ser Gly Phe Lys Phe Ser Arg Tyr
20 25 30

Ala Met Ser Trp Val Arg Gln Thr Pro Glu Lys Arg Leu Glu Trp Val
35 40 45

Ala Thr Ile Ser Ser Gly Gly Ser Tyr Ile Tyr Tyr Pro Asp Ser Val
50 55 60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Val Lys Asn Thr Leu Tyr
65 70 75 80

Leu Gln Met Ser Ser Leu Arg Ser Glu Asp Thr Ala Met Tyr Tyr Cys
85 90 95

Ala Arg Arg Asp Tyr Asp Leu Asp Tyr Phe Asp Ser Trp Gly Gln Gly
100 105 110

Thr Thr Leu Thr Val Ser Ser
115

<210> SEQ ID NO 69
<211> LENGTH: 109
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic polypeptide"

<400> SEQUENCE: 69

Asp Ile Lys Met Thr Gln Ser Pro Ser Ser Met Tyr Ala Ser Leu Gly
1 5 10 15

Glu Arg Val Thr Ile Thr Cys Lys Ala Ser Arg Asp Ile Arg Ser Tyr
20 25 30

Leu Thr Trp Tyr Gln Gln Lys Pro Trp Lys Ser Pro Lys Thr Leu Ile
35 40 45

Tyr Tyr Ala Thr Ser Leu Ala Asp Gly Val Pro Ser Arg Phe Ser Gly
50 55 60

Ser Gly Ser Gly Gln Asp Tyr Ser Leu Thr Ile Ser Ser Leu Glu Ser
65 70 75 80

Asp Asp Thr Ala Thr Tyr Tyr Cys Leu Gln His Gly Glu Ser Pro Phe
85 90 95

Thr Phe Gly Ser Gly Thr Lys Leu Glu Ile Lys Arg Ala
100 105

<210> SEQ ID NO 70
<211> LENGTH: 22
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic peptide"

<400> SEQUENCE: 70

Met Leu Leu Leu Val Thr Ser Leu Leu Leu Cys Glu Leu Pro His Pro
1 5 10 15

Ala Phe Leu Leu Ile Pro

-continued

20

<210> SEQ ID NO 71
<211> LENGTH: 24
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence: Synthetic peptide"

<400> SEQUENCE: 71

Leu Glu Gly Gly Gly Glu Gly Arg Gly Ser Leu Leu Thr Cys Gly Asp
1 5 10 15

Val Glu Glu Asn Pro Gly Pro Arg
20

<210> SEQ ID NO 72
<211> LENGTH: 323
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> SEQUENCE: 72

Met Pro Pro Pro Arg Leu Leu Phe Phe Leu Leu Phe Leu Thr Pro Met
1 5 10 15

Glu Val Arg Pro Glu Glu Pro Leu Val Val Lys Val Glu Glu Gly Asp
20 25 30

Asn Ala Val Leu Gln Cys Leu Lys Gly Thr Ser Asp Gly Pro Thr Gln
35 40 45

Gln Leu Thr Trp Ser Arg Glu Ser Pro Leu Lys Pro Phe Leu Lys Leu
50 55 60

Ser Leu Gly Leu Pro Gly Leu Gly Ile His Met Arg Pro Leu Ala Ile
65 70 75 80

Trp Leu Phe Ile Phe Asn Val Ser Gln Gln Met Gly Gly Phe Tyr Leu
85 90 95

Cys Gln Pro Gly Pro Pro Ser Glu Lys Ala Trp Gln Pro Gly Trp Thr
100 105 110

Val Asn Val Glu Gly Ser Gly Glu Leu Phe Arg Trp Asn Val Ser Asp
115 120 125

Leu Gly Gly Leu Gly Cys Gly Leu Lys Asn Arg Ser Ser Glu Gly Pro
130 135 140

Ser Ser Pro Ser Gly Lys Leu Met Ser Pro Lys Leu Tyr Val Trp Ala
145 150 155 160

Lys Asp Arg Pro Glu Ile Trp Glu Gly Glu Pro Pro Cys Val Pro Pro
165 170 175

Arg Asp Ser Leu Asn Gln Ser Leu Ser Gln Asp Leu Thr Met Ala Pro
180 185 190

Gly Ser Thr Leu Trp Leu Ser Cys Gly Val Pro Pro Asp Ser Val Ser
195 200 205

Arg Gly Pro Leu Ser Trp Thr His Val His Pro Lys Gly Pro Lys Ser
210 215 220

Leu Leu Ser Leu Glu Leu Lys Asp Asp Arg Pro Ala Arg Asp Met Trp
225 230 235 240

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```
Val Met Glu Thr Gly Leu Leu Leu Pro Arg Ala Thr Ala Gln Asp Ala
                245                 250                 255

Gly Lys Tyr Tyr Cys His Arg Gly Asn Leu Thr Met Ser Phe His Leu
            260                 265                 270

Glu Ile Thr Ala Arg Pro Val Leu Trp His Trp Leu Leu Arg Thr Gly
        275                 280                 285

Gly Trp Lys Val Ser Ala Val Thr Leu Ala Tyr Leu Ile Phe Cys Leu
    290                 295                 300

Cys Ser Leu Val Gly Ile Leu His Leu Gln Arg Ala Leu Val Leu Arg
305                 310                 315                 320

Arg Lys Arg


<210> SEQ ID NO 73
<211> LENGTH: 244
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
      Synthetic polypeptide"

<400> SEQUENCE: 73

Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Lys Pro Gly Gly
1               5                   10                  15

Ser Leu Lys Leu Ser Cys Ala Ala Ser Gly Phe Lys Phe Ser Arg Tyr
            20                  25                  30

Ala Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
        35                  40                  45

Ala Thr Ile Ser Ser Gly Gly Ser Tyr Ile Tyr Tyr Pro Asp Ser Val
    50                  55                  60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Val Lys Asn Thr Leu Tyr
65                  70                  75                  80

Leu Gln Met Ser Ser Leu Arg Ser Glu Asp Thr Ala Met Tyr Tyr Cys
                85                  90                  95

Ala Arg Arg Asp Tyr Asp Leu Asp Tyr Phe Asp Ser Trp Gly Gln Gly
            100                 105                 110

Thr Leu Val Thr Val Ser Ser Gly Ser Thr Ser Gly Gly Gly Ser Gly
        115                 120                 125

Gly Gly Ser Gly Gly Gly Gly Ser Gly Asp Ile Gln Met Thr Gln Ser
    130                 135                 140

Pro Ser Ser Leu Ser Ala Ser Val Gly Asp Arg Val Thr Ile Thr Cys
145                 150                 155                 160

Lys Ala Ser Arg Asp Ile Arg Ser Tyr Leu Thr Trp Tyr Gln Gln Lys
                165                 170                 175

Pro Gly Lys Ala Pro Lys Thr Leu Ile Tyr Tyr Ala Thr Ser Leu Ala
            180                 185                 190

Asp Gly Val Pro Ser Arg Phe Ser Gly Ser Gly Ser Gly Gln Asp Tyr
        195                 200                 205

Ser Leu Thr Ile Ser Ser Leu Glu Ser Asp Asp Thr Ala Thr Tyr Tyr
    210                 215                 220

Cys Leu Gln His Gly Glu Ser Pro Phe Thr Phe Gly Ser Gly Thr Lys
225                 230                 235                 240

Met Glu Ile Lys
```

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<210> SEQ ID NO 74

<400> SEQUENCE: 74

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<210> SEQ ID NO 75
<211> LENGTH: 68
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic polypeptide"

<400> SEQUENCE: 75

Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly Asp
1 5 10 15

Arg Val Thr Ile Thr Cys Lys Ala Ser Arg Asp Ile Arg Ser Tyr Leu
20 25 30

Thr Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Thr Leu Ile Tyr
35 40 45

Tyr Ala Thr Ser Leu Ala Asp Gly Val Pro Ser Arg Phe Ser Gly Ser
50 55 60

Gly Ser Gly Gln
65

<210> SEQ ID NO 76
<211> LENGTH: 32
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic polypeptide"

<400> SEQUENCE: 76

Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
1 5 10 15

Asp Arg Val Thr Ile Thr Cys Lys Ala Ser Arg Asp Ile Arg Ser Tyr
20 25 30

<210> SEQ ID NO 77
<211> LENGTH: 65
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic polypeptide"

<400> SEQUENCE: 77

Leu Thr Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Thr Leu Ile
1 5 10 15

Tyr Tyr Ala Thr Ser Leu Ala Asp Gly Val Pro Ser Arg Phe Ser Gly
20 25 30

Ser Gly Ser Gly Gln Asp Tyr Ser Leu Thr Ile Ser Ser Leu Glu Ser
35 40 45

Asp Asp Thr Ala Thr Tyr Tyr Cys Leu Gln His Gly Glu Ser Pro Phe
50 55 60

-continued

Thr
65

<210> SEQ ID NO 78
<211> LENGTH: 12
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic peptide"

<400> SEQUENCE: 78

Phe Gly Ser Gly Thr Lys Leu Glu Ile Lys Arg Ala
1 5 10

<210> SEQ ID NO 79
<211> LENGTH: 35
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic polypeptide"

<400> SEQUENCE: 79

Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Lys Pro Gly Gly
1 5 10 15

Ser Leu Lys Leu Ser Cys Ala Ala Ser Gly Phe Lys Phe Ser Arg Tyr
20 25 30

Ala Met Ser
35

<210> SEQ ID NO 80
<211> LENGTH: 20
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic peptide"

<400> SEQUENCE: 80

Trp Val Arg Gln Ala Pro Gly Lys Arg Leu Glu Trp Val Ala Thr Ile
1 5 10 15

Ser Ser Gly Gly
20

<210> SEQ ID NO 81
<211> LENGTH: 53
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic polypeptide"

<400> SEQUENCE: 81

Ser Tyr Ile Tyr Tyr Pro Asp Ser Val Lys Gly Arg Phe Thr Ile Ser
1 5 10 15

Arg Asp Asn Val Lys Asn Thr Leu Tyr Leu Gln Met Ser Ser Leu Arg
20 25 30

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Ser Glu Asp Thr Ala Met Tyr Tyr Cys Ala Arg Arg Asp Tyr Asp Leu
35 40 45

Asp Tyr Phe Asp Ser
50

<210> SEQ ID NO 82
<211> LENGTH: 11
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence: Synthetic peptide"

<400> SEQUENCE: 82

Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser
1 5 10

<210> SEQ ID NO 83
<211> LENGTH: 653
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> SEQUENCE: 83

Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Lys Pro Gly Gly
1 5 10 15

Ser Leu Lys Leu Ser Cys Ala Ala Ser Gly Phe Lys Phe Ser Arg Tyr
20 25 30

Ala Met Ser Trp Val Arg Gln Ala Pro Gly Lys Arg Leu Glu Trp Val
35 40 45

Ala Thr Ile Ser Ser Gly Gly Ser Tyr Ile Tyr Tyr Pro Asp Ser Val
50 55 60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Val Lys Asn Thr Leu Tyr
65 70 75 80

Leu Gln Met Ser Ser Leu Arg Ser Glu Asp Thr Ala Met Tyr Tyr Cys
85 90 95

Ala Arg Arg Asp Tyr Asp Leu Asp Tyr Phe Asp Ser Trp Gly Gln Gly
100 105 110

Thr Leu Val Thr Val Ser Ser Gly Ser Thr Ser Gly Gly Gly Ser Gly
115 120 125

Gly Gly Ser Gly Gly Gly Gly Ser Ser Asp Ile Gln Met Thr Gln Ser
130 135 140

Pro Ser Ser Leu Ser Ala Ser Val Gly Asp Arg Val Thr Ile Thr Cys
145 150 155 160

Lys Ala Ser Arg Asp Ile Arg Ser Tyr Leu Thr Trp Tyr Gln Gln Lys
165 170 175

Pro Gly Lys Ala Pro Lys Thr Leu Ile Tyr Tyr Ala Thr Ser Leu Ala
180 185 190

Asp Gly Val Pro Ser Arg Phe Ser Gly Ser Gly Ser Gly Gln Asp Tyr
195 200 205

Ser Leu Thr Ile Ser Ser Leu Glu Ser Asp Asp Thr Ala Thr Tyr Tyr
210 215 220

Cys Leu Gln His Gly Glu Ser Pro Phe Thr Phe Gly Ser Gly Thr Lys

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225                 230                 235                 240

Leu Glu Ile Lys Arg Ala Glu Ser Lys Tyr Gly Pro Pro Cys Pro Pro
                245                 250                 255

Cys Pro Ala Pro Glu Phe Glu Gly Gly Pro Ser Val Phe Leu Phe Pro
            260                 265                 270

Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr
        275                 280                 285

Cys Val Val Val Asp Val Ser Gln Glu Asp Pro Glu Val Gln Phe Asn
    290                 295                 300

Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg
305                 310                 315                 320

Glu Glu Gln Phe Gln Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val
                325                 330                 335

Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser
            340                 345                 350

Asn Lys Gly Leu Pro Ser Ser Ile Glu Lys Thr Ile Ser Lys Ala Lys
        355                 360                 365

Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Gln Glu
    370                 375                 380

Glu Met Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe
385                 390                 395                 400

Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu
                405                 410                 415

Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe
            420                 425                 430

Phe Leu Tyr Ser Arg Leu Thr Val Asp Lys Ser Arg Trp Gln Glu Gly
        435                 440                 445

Asn Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr
    450                 455                 460

Thr Gln Lys Ser Leu Ser Leu Ser Leu Gly Lys Met Ala Leu Ile Val
465                 470                 475                 480

Leu Gly Gly Val Ala Gly Leu Leu Leu Phe Ile Gly Leu Gly Ile Phe
                485                 490                 495

Phe Ala Val Ser Leu Ser Lys Met Leu Lys Lys Arg Ser Pro Leu Thr
            500                 505                 510

Thr Gly Val Tyr Val Lys Met Pro Pro Thr Glu Pro Glu Cys Glu Lys
        515                 520                 525

Gln Phe Gln Pro Tyr Phe Ile Pro Ile Asn Gly Gly Gly Arg Val Lys
    530                 535                 540

Phe Ser Arg Ser Ala Asp Ala Pro Ala Tyr Gln Gln Gly Gln Asn Gln
545                 550                 555                 560

Leu Tyr Asn Glu Leu Asn Leu Gly Arg Arg Glu Glu Tyr Asp Val Leu
                565                 570                 575

Asp Lys Arg Arg Gly Arg Asp Pro Glu Met Gly Gly Lys Pro Arg Arg
            580                 585                 590

Lys Asn Pro Gln Glu Gly Leu Tyr Asn Glu Leu Gln Lys Asp Lys Met
        595                 600                 605

Ala Glu Ala Tyr Ser Glu Ile Gly Met Lys Gly Glu Arg Arg Arg Gly
    610                 615                 620

Lys Gly His Asp Gly Leu Tyr Gln Gly Leu Ser Thr Ala Thr Lys Asp
625                 630                 635                 640
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Thr Tyr Asp Ala Leu His Met Gln Ala Leu Pro Pro Arg
                645                 650


<210> SEQ ID NO 84
<211> LENGTH: 675
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
      Synthetic polypeptide"

<400> SEQUENCE: 84

Met Leu Leu Leu Val Thr Ser Leu Leu Leu Cys Glu Leu Pro His Pro
1               5                   10                  15

Ala Phe Leu Leu Ile Pro Glu Val Gln Leu Val Glu Ser Gly Gly Gly
            20                  25                  30

Leu Val Lys Pro Gly Gly Ser Leu Lys Leu Ser Cys Ala Ala Ser Gly
        35                  40                  45

Phe Lys Phe Ser Arg Tyr Ala Met Ser Trp Val Arg Gln Ala Pro Gly
    50                  55                  60

Lys Arg Leu Glu Trp Val Ala Thr Ile Ser Ser Gly Gly Ser Tyr Ile
65                  70                  75                  80

Tyr Tyr Pro Asp Ser Val Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn
                85                  90                  95

Val Lys Asn Thr Leu Tyr Leu Gln Met Ser Ser Leu Arg Ser Glu Asp
            100                 105                 110

Thr Ala Met Tyr Tyr Cys Ala Arg Arg Asp Tyr Asp Leu Asp Tyr Phe
        115                 120                 125

Asp Ser Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser Gly Ser Thr
    130                 135                 140

Ser Gly Gly Gly Ser Gly Gly Gly Ser Gly Gly Gly Gly Ser Ser Asp
145                 150                 155                 160

Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly Asp
                165                 170                 175

Arg Val Thr Ile Thr Cys Lys Ala Ser Arg Asp Ile Arg Ser Tyr Leu
            180                 185                 190

Thr Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Thr Leu Ile Tyr
        195                 200                 205

Tyr Ala Thr Ser Leu Ala Asp Gly Val Pro Ser Arg Phe Ser Gly Ser
    210                 215                 220

Gly Ser Gly Gln Asp Tyr Ser Leu Thr Ile Ser Ser Leu Glu Ser Asp
225                 230                 235                 240

Asp Thr Ala Thr Tyr Tyr Cys Leu Gln His Gly Glu Ser Pro Phe Thr
                245                 250                 255

Phe Gly Ser Gly Thr Lys Leu Glu Ile Lys Arg Ala Glu Ser Lys Tyr
            260                 265                 270

Gly Pro Pro Cys Pro Pro Cys Pro Ala Pro Glu Phe Glu Gly Gly Pro
        275                 280                 285

Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser
    290                 295                 300

Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser Gln Glu Asp
305                 310                 315                 320
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Pro Glu Val Gln Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn
                325                 330                 335

Ala Lys Thr Lys Pro Arg Glu Glu Gln Phe Gln Ser Thr Tyr Arg Val
            340                 345                 350

Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu
        355                 360                 365

Tyr Lys Cys Lys Val Ser Asn Lys Gly Leu Pro Ser Ser Ile Glu Lys
    370                 375                 380

Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr
385                 390                 395                 400

Leu Pro Pro Ser Gln Glu Glu Met Thr Lys Asn Gln Val Ser Leu Thr
                405                 410                 415

Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu
            420                 425                 430

Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu
        435                 440                 445

Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Arg Leu Thr Val Asp Lys
    450                 455                 460

Ser Arg Trp Gln Glu Gly Asn Val Phe Ser Cys Ser Val Met His Glu
465                 470                 475                 480

Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Leu Gly
                485                 490                 495

Lys Met Ala Leu Ile Val Leu Gly Gly Val Ala Gly Leu Leu Leu Phe
            500                 505                 510

Ile Gly Leu Gly Ile Phe Phe Ala Val Ser Leu Ser Lys Met Leu Lys
        515                 520                 525

Lys Arg Ser Pro Leu Thr Thr Gly Val Tyr Val Lys Met Pro Pro Thr
    530                 535                 540

Glu Pro Glu Cys Glu Lys Gln Phe Gln Pro Tyr Phe Ile Pro Ile Asn
545                 550                 555                 560

Gly Gly Gly Arg Val Lys Phe Ser Arg Ser Ala Asp Ala Pro Ala Tyr
                565                 570                 575

Gln Gln Gly Gln Asn Gln Leu Tyr Asn Glu Leu Asn Leu Gly Arg Arg
            580                 585                 590

Glu Glu Tyr Asp Val Leu Asp Lys Arg Arg Gly Arg Asp Pro Glu Met
        595                 600                 605

Gly Gly Lys Pro Arg Arg Lys Asn Pro Gln Glu Gly Leu Tyr Asn Glu
    610                 615                 620

Leu Gln Lys Asp Lys Met Ala Glu Ala Tyr Ser Glu Ile Gly Met Lys
625                 630                 635                 640

Gly Glu Arg Arg Arg Gly Lys Gly His Asp Gly Leu Tyr Gln Gly Leu
                645                 650                 655

Ser Thr Ala Thr Lys Asp Thr Tyr Asp Ala Leu His Met Gln Ala Leu
            660                 665                 670

Pro Pro Arg
        675


<210> SEQ ID NO 85
<211> LENGTH: 653
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
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<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic polypeptide"

<400> SEQUENCE: 85

Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
1 5 10 15

Asp Arg Val Thr Ile Thr Cys Lys Ala Ser Arg Asp Ile Arg Ser Tyr
20 25 30

Leu Thr Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Thr Leu Ile
35 40 45

Tyr Tyr Ala Thr Ser Leu Ala Asp Gly Val Pro Ser Arg Phe Ser Gly
50 55 60

Ser Gly Ser Gly Gln Asp Tyr Ser Leu Thr Ile Ser Ser Leu Glu Ser
65 70 75 80

Asp Asp Thr Ala Thr Tyr Tyr Cys Leu Gln His Gly Glu Ser Pro Phe
85 90 95

Thr Phe Gly Ser Gly Thr Lys Leu Glu Ile Lys Arg Ala Gly Ser Thr
100 105 110

Ser Gly Gly Gly Ser Gly Gly Gly Ser Gly Gly Gly Gly Ser Ser Glu
115 120 125

Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Lys Pro Gly Gly Ser
130 135 140

Leu Lys Leu Ser Cys Ala Ala Ser Gly Phe Lys Phe Ser Arg Tyr Ala
145 150 155 160

Met Ser Trp Val Arg Gln Ala Pro Gly Lys Arg Leu Glu Trp Val Ala
165 170 175

Thr Ile Ser Ser Gly Gly Ser Tyr Ile Tyr Tyr Pro Asp Ser Val Lys
180 185 190

Gly Arg Phe Thr Ile Ser Arg Asp Asn Val Lys Asn Thr Leu Tyr Leu
195 200 205

Gln Met Ser Ser Leu Arg Ser Glu Asp Thr Ala Met Tyr Tyr Cys Ala
210 215 220

Arg Arg Asp Tyr Asp Leu Asp Tyr Phe Asp Ser Trp Gly Gln Gly Thr
225 230 235 240

Leu Val Thr Val Ser Ser Glu Ser Lys Tyr Gly Pro Pro Cys Pro Pro
245 250 255

Cys Pro Ala Pro Glu Phe Glu Gly Gly Pro Ser Val Phe Leu Phe Pro
260 265 270

Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr
275 280 285

Cys Val Val Val Asp Val Ser Gln Glu Asp Pro Glu Val Gln Phe Asn
290 295 300

Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg
305 310 315 320

Glu Glu Gln Phe Gln Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val
325 330 335

Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser
340 345 350

Asn Lys Gly Leu Pro Ser Ser Ile Glu Lys Thr Ile Ser Lys Ala Lys
355 360 365

Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Gln Glu
370 375 380

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Glu Met Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe
385                 390                 395                 400

Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu
                405                 410                 415

Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe
            420                 425                 430

Phe Leu Tyr Ser Arg Leu Thr Val Asp Lys Ser Arg Trp Gln Glu Gly
        435                 440                 445

Asn Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr
    450                 455                 460

Thr Gln Lys Ser Leu Ser Leu Ser Leu Gly Lys Met Ala Leu Ile Val
465                 470                 475                 480

Leu Gly Gly Val Ala Gly Leu Leu Leu Phe Ile Gly Leu Gly Ile Phe
                485                 490                 495

Phe Ala Val Ser Leu Ser Lys Met Leu Lys Lys Arg Ser Pro Leu Thr
            500                 505                 510

Thr Gly Val Tyr Val Lys Met Pro Pro Thr Glu Pro Glu Cys Glu Lys
        515                 520                 525

Gln Phe Gln Pro Tyr Phe Ile Pro Ile Asn Gly Gly Gly Arg Val Lys
    530                 535                 540

Phe Ser Arg Ser Ala Asp Ala Pro Ala Tyr Gln Gln Gly Gln Asn Gln
545                 550                 555                 560

Leu Tyr Asn Glu Leu Asn Leu Gly Arg Arg Glu Glu Tyr Asp Val Leu
                565                 570                 575

Asp Lys Arg Arg Gly Arg Asp Pro Glu Met Gly Gly Lys Pro Arg Arg
            580                 585                 590

Lys Asn Pro Gln Glu Gly Leu Tyr Asn Glu Leu Gln Lys Asp Lys Met
        595                 600                 605

Ala Glu Ala Tyr Ser Glu Ile Gly Met Lys Gly Glu Arg Arg Arg Gly
    610                 615                 620

Lys Gly His Asp Gly Leu Tyr Gln Gly Leu Ser Thr Ala Thr Lys Asp
625                 630                 635                 640

Thr Tyr Asp Ala Leu His Met Gln Ala Leu Pro Pro Arg
                645                 650


<210> SEQ ID NO 86
<211> LENGTH: 675
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
      Synthetic polypeptide"

<400> SEQUENCE: 86

Met Leu Leu Leu Val Thr Ser Leu Leu Leu Cys Glu Leu Pro His Pro
1               5                   10                  15

Ala Phe Leu Leu Ile Pro Asp Ile Gln Met Thr Gln Ser Pro Ser Ser
            20                  25                  30

Leu Ser Ala Ser Val Gly Asp Arg Val Thr Ile Thr Cys Lys Ala Ser
        35                  40                  45

Arg Asp Ile Arg Ser Tyr Leu Thr Trp Tyr Gln Gln Lys Pro Gly Lys
    50                  55                  60
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Ala Pro Lys Thr Leu Ile Tyr Tyr Ala Thr Ser Leu Ala Asp Gly Val
65                  70                  75                  80

Pro Ser Arg Phe Ser Gly Ser Gly Ser Gly Gln Asp Tyr Ser Leu Thr
                85                  90                  95

Ile Ser Ser Leu Glu Ser Asp Asp Thr Ala Thr Tyr Tyr Cys Leu Gln
            100                 105                 110

His Gly Glu Ser Pro Phe Thr Phe Gly Ser Gly Thr Lys Leu Glu Ile
        115                 120                 125

Lys Arg Ala Gly Ser Thr Ser Gly Gly Gly Ser Gly Gly Gly Ser Gly
    130                 135                 140

Gly Gly Gly Ser Ser Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu
145                 150                 155                 160

Val Lys Pro Gly Gly Ser Leu Lys Leu Ser Cys Ala Ala Ser Gly Phe
                165                 170                 175

Lys Phe Ser Arg Tyr Ala Met Ser Trp Val Arg Gln Ala Pro Gly Lys
            180                 185                 190

Arg Leu Glu Trp Val Ala Thr Ile Ser Ser Gly Gly Ser Tyr Ile Tyr
        195                 200                 205

Tyr Pro Asp Ser Val Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Val
    210                 215                 220

Lys Asn Thr Leu Tyr Leu Gln Met Ser Ser Leu Arg Ser Glu Asp Thr
225                 230                 235                 240

Ala Met Tyr Tyr Cys Ala Arg Arg Asp Tyr Asp Leu Asp Tyr Phe Asp
                245                 250                 255

Ser Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser Glu Ser Lys Tyr
            260                 265                 270

Gly Pro Pro Cys Pro Pro Cys Pro Ala Pro Glu Phe Glu Gly Gly Pro
        275                 280                 285

Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser
    290                 295                 300

Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser Gln Glu Asp
305                 310                 315                 320

Pro Glu Val Gln Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn
                325                 330                 335

Ala Lys Thr Lys Pro Arg Glu Glu Gln Phe Gln Ser Thr Tyr Arg Val
            340                 345                 350

Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu
        355                 360                 365

Tyr Lys Cys Lys Val Ser Asn Lys Gly Leu Pro Ser Ser Ile Glu Lys
    370                 375                 380

Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr
385                 390                 395                 400

Leu Pro Pro Ser Gln Glu Glu Met Thr Lys Asn Gln Val Ser Leu Thr
                405                 410                 415

Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu
            420                 425                 430

Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu
        435                 440                 445

Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Arg Leu Thr Val Asp Lys
    450                 455                 460

Ser Arg Trp Gln Glu Gly Asn Val Phe Ser Cys Ser Val Met His Glu
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465                 470                 475                 480

Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Leu Gly
                485                 490                 495

Lys Met Ala Leu Ile Val Leu Gly Gly Val Ala Gly Leu Leu Leu Phe
            500                 505                 510

Ile Gly Leu Gly Ile Phe Phe Ala Val Ser Leu Ser Lys Met Leu Lys
        515                 520                 525

Lys Arg Ser Pro Leu Thr Thr Gly Val Tyr Val Lys Met Pro Pro Thr
    530                 535                 540

Glu Pro Glu Cys Glu Lys Gln Phe Gln Pro Tyr Phe Ile Pro Ile Asn
545                 550                 555                 560

Gly Gly Gly Arg Val Lys Phe Ser Arg Ser Ala Asp Ala Pro Ala Tyr
                565                 570                 575

Gln Gln Gly Gln Asn Gln Leu Tyr Asn Glu Leu Asn Leu Gly Arg Arg
            580                 585                 590

Glu Glu Tyr Asp Val Leu Asp Lys Arg Arg Gly Arg Asp Pro Glu Met
        595                 600                 605

Gly Gly Lys Pro Arg Arg Lys Asn Pro Gln Glu Gly Leu Tyr Asn Glu
    610                 615                 620

Leu Gln Lys Asp Lys Met Ala Glu Ala Tyr Ser Glu Ile Gly Met Lys
625                 630                 635                 640

Gly Glu Arg Arg Arg Gly Lys Gly His Asp Gly Leu Tyr Gln Gly Leu
                645                 650                 655

Ser Thr Ala Thr Lys Asp Thr Tyr Asp Ala Leu His Met Gln Ala Leu
            660                 665                 670

Pro Pro Arg
        675


<210> SEQ ID NO 87
<211> LENGTH: 654
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
      Synthetic polypeptide"

<400> SEQUENCE: 87

Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Lys Pro Gly Gly
1               5                   10                  15

Ser Leu Lys Leu Ser Cys Ala Ala Ser Gly Phe Lys Phe Ser Arg Tyr
            20                  25                  30

Ala Met Ser Trp Val Arg Gln Ala Pro Gly Lys Arg Leu Glu Trp Val
        35                  40                  45

Ala Thr Ile Ser Ser Gly Gly Ser Tyr Ile Tyr Tyr Pro Asp Ser Val
    50                  55                  60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Val Lys Asn Thr Leu Tyr
65                  70                  75                  80

Leu Gln Met Ser Ser Leu Arg Ser Glu Asp Thr Ala Met Tyr Tyr Cys
                85                  90                  95

Ala Arg Arg Asp Tyr Asp Leu Asp Tyr Phe Asp Ser Trp Gly Gln Gly
            100                 105                 110

Thr Leu Val Thr Val Ser Ser Gly Ser Thr Ser Gly Gly Gly Ser Gly
        115                 120                 125
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Gly Gly Ser Gly Gly Gly Gly Ser Ser Asp Ile Gln Met Thr Gln Ser
    130                 135                 140

Pro Ser Ser Leu Ser Ala Ser Val Gly Asp Arg Val Thr Ile Thr Cys
145                 150                 155                 160

Lys Ala Ser Arg Asp Ile Arg Ser Tyr Leu Thr Trp Tyr Gln Gln Lys
                165                 170                 175

Pro Gly Lys Ala Pro Lys Thr Leu Ile Tyr Tyr Ala Thr Ser Leu Ala
            180                 185                 190

Asp Gly Val Pro Ser Arg Phe Ser Gly Ser Gly Ser Gly Gln Asp Tyr
        195                 200                 205

Ser Leu Thr Ile Ser Ser Leu Glu Ser Asp Asp Thr Ala Thr Tyr Tyr
    210                 215                 220

Cys Leu Gln His Gly Glu Ser Pro Phe Thr Phe Gly Ser Gly Thr Lys
225                 230                 235                 240

Leu Glu Ile Lys Arg Ala Glu Ser Lys Tyr Gly Pro Pro Cys Pro Pro
                245                 250                 255

Cys Pro Ala Pro Glu Phe Glu Gly Gly Pro Ser Val Phe Leu Phe Pro
            260                 265                 270

Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr
        275                 280                 285

Cys Val Val Val Asp Val Ser Gln Glu Asp Pro Glu Val Gln Phe Asn
    290                 295                 300

Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg
305                 310                 315                 320

Glu Glu Gln Phe Gln Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val
                325                 330                 335

Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser
            340                 345                 350

Asn Lys Gly Leu Pro Ser Ser Ile Glu Lys Thr Ile Ser Lys Ala Lys
        355                 360                 365

Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Gln Glu
    370                 375                 380

Glu Met Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe
385                 390                 395                 400

Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu
                405                 410                 415

Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe
            420                 425                 430

Phe Leu Tyr Ser Arg Leu Thr Val Asp Lys Ser Arg Trp Gln Glu Gly
        435                 440                 445

Asn Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr
    450                 455                 460

Thr Gln Lys Ser Leu Ser Leu Ser Leu Gly Lys Met Ala Leu Ile Val
465                 470                 475                 480

Leu Gly Gly Val Ala Gly Leu Leu Leu Phe Ile Gly Leu Gly Ile Phe
                485                 490                 495

Phe Lys Arg Gly Arg Lys Lys Leu Leu Tyr Ile Phe Lys Gln Pro Phe
            500                 505                 510

Met Arg Pro Val Gln Thr Thr Gln Glu Glu Asp Gly Cys Ser Cys Arg
        515                 520                 525
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Phe Pro Glu Glu Glu Glu Gly Gly Cys Glu Leu Gly Gly Gly Arg Val
    530                 535                 540

Lys Phe Ser Arg Ser Ala Asp Ala Pro Ala Tyr Gln Gln Gly Gln Asn
545                 550                 555                 560

Gln Leu Tyr Asn Glu Leu Asn Leu Gly Arg Arg Glu Glu Tyr Asp Val
                565                 570                 575

Leu Asp Lys Arg Arg Gly Arg Asp Pro Glu Met Gly Gly Lys Pro Arg
            580                 585                 590

Arg Lys Asn Pro Gln Glu Gly Leu Tyr Asn Glu Leu Gln Lys Asp Lys
        595                 600                 605

Met Ala Glu Ala Tyr Ser Glu Ile Gly Met Lys Gly Glu Arg Arg Arg
    610                 615                 620

Gly Lys Gly His Asp Gly Leu Tyr Gln Gly Leu Ser Thr Ala Thr Lys
625                 630                 635                 640

Asp Thr Tyr Asp Ala Leu His Met Gln Ala Leu Pro Pro Arg
                645                 650


<210> SEQ ID NO 88
<211> LENGTH: 676
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
      Synthetic polypeptide"

<400> SEQUENCE: 88

Met Leu Leu Leu Val Thr Ser Leu Leu Leu Cys Glu Leu Pro His Pro
1               5                   10                  15

Ala Phe Leu Leu Ile Pro Glu Val Gln Leu Val Glu Ser Gly Gly Gly
            20                  25                  30

Leu Val Lys Pro Gly Gly Ser Leu Lys Leu Ser Cys Ala Ala Ser Gly
        35                  40                  45

Phe Lys Phe Ser Arg Tyr Ala Met Ser Trp Val Arg Gln Ala Pro Gly
    50                  55                  60

Lys Arg Leu Glu Trp Val Ala Thr Ile Ser Ser Gly Gly Ser Tyr Ile
65                  70                  75                  80

Tyr Tyr Pro Asp Ser Val Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn
                85                  90                  95

Val Lys Asn Thr Leu Tyr Leu Gln Met Ser Ser Leu Arg Ser Glu Asp
            100                 105                 110

Thr Ala Met Tyr Tyr Cys Ala Arg Arg Asp Tyr Asp Leu Asp Tyr Phe
        115                 120                 125

Asp Ser Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser Gly Ser Thr
    130                 135                 140

Ser Gly Gly Gly Ser Gly Gly Gly Ser Gly Gly Gly Gly Ser Ser Asp
145                 150                 155                 160

Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly Asp
                165                 170                 175

Arg Val Thr Ile Thr Cys Lys Ala Ser Arg Asp Ile Arg Ser Tyr Leu
            180                 185                 190

Thr Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Thr Leu Ile Tyr
        195                 200                 205

Tyr Ala Thr Ser Leu Ala Asp Gly Val Pro Ser Arg Phe Ser Gly Ser
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    210                 215                 220

Gly Ser Gly Gln Asp Tyr Ser Leu Thr Ile Ser Ser Leu Glu Ser Asp
225                 230                 235                 240

Asp Thr Ala Thr Tyr Tyr Cys Leu Gln His Gly Glu Ser Pro Phe Thr
                245                 250                 255

Phe Gly Ser Gly Thr Lys Leu Glu Ile Lys Arg Ala Glu Ser Lys Tyr
            260                 265                 270

Gly Pro Pro Cys Pro Pro Cys Pro Ala Pro Glu Phe Glu Gly Gly Pro
        275                 280                 285

Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser
    290                 295                 300

Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser Gln Glu Asp
305                 310                 315                 320

Pro Glu Val Gln Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn
                325                 330                 335

Ala Lys Thr Lys Pro Arg Glu Glu Gln Phe Gln Ser Thr Tyr Arg Val
            340                 345                 350

Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu
        355                 360                 365

Tyr Lys Cys Lys Val Ser Asn Lys Gly Leu Pro Ser Ser Ile Glu Lys
    370                 375                 380

Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr
385                 390                 395                 400

Leu Pro Pro Ser Gln Glu Glu Met Thr Lys Asn Gln Val Ser Leu Thr
                405                 410                 415

Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu
            420                 425                 430

Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu
        435                 440                 445

Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Arg Leu Thr Val Asp Lys
    450                 455                 460

Ser Arg Trp Gln Glu Gly Asn Val Phe Ser Cys Ser Val Met His Glu
465                 470                 475                 480

Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Leu Gly
                485                 490                 495

Lys Met Ala Leu Ile Val Leu Gly Gly Val Ala Gly Leu Leu Leu Phe
            500                 505                 510

Ile Gly Leu Gly Ile Phe Phe Lys Arg Gly Arg Lys Lys Leu Leu Tyr
        515                 520                 525

Ile Phe Lys Gln Pro Phe Met Arg Pro Val Gln Thr Thr Gln Glu Glu
    530                 535                 540

Asp Gly Cys Ser Cys Arg Phe Pro Glu Glu Glu Glu Gly Gly Cys Glu
545                 550                 555                 560

Leu Gly Gly Gly Arg Val Lys Phe Ser Arg Ser Ala Asp Ala Pro Ala
                565                 570                 575

Tyr Gln Gln Gly Gln Asn Gln Leu Tyr Asn Glu Leu Asn Leu Gly Arg
            580                 585                 590

Arg Glu Glu Tyr Asp Val Leu Asp Lys Arg Arg Gly Arg Asp Pro Glu
        595                 600                 605

Met Gly Gly Lys Pro Arg Arg Lys Asn Pro Gln Glu Gly Leu Tyr Asn
    610                 615                 620
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Glu Leu Gln Lys Asp Lys Met Ala Glu Ala Tyr Ser Glu Ile Gly Met
625                 630                 635                 640

Lys Gly Glu Arg Arg Arg Gly Lys Gly His Asp Gly Leu Tyr Gln Gly
                645                 650                 655

Leu Ser Thr Ala Thr Lys Asp Thr Tyr Asp Ala Leu His Met Gln Ala
            660                 665                 670

Leu Pro Pro Arg
        675


<210> SEQ ID NO 89
<211> LENGTH: 654
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
      Synthetic polypeptide"

<400> SEQUENCE: 89

Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
1               5                   10                  15

Asp Arg Val Thr Ile Thr Cys Lys Ala Ser Arg Asp Ile Arg Ser Tyr
            20                  25                  30

Leu Thr Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Thr Leu Ile
        35                  40                  45

Tyr Tyr Ala Thr Ser Leu Ala Asp Gly Val Pro Ser Arg Phe Ser Gly
    50                  55                  60

Ser Gly Ser Gly Gln Asp Tyr Ser Leu Thr Ile Ser Ser Leu Glu Ser
65                  70                  75                  80

Asp Asp Thr Ala Thr Tyr Tyr Cys Leu Gln His Gly Glu Ser Pro Phe
                85                  90                  95

Thr Phe Gly Ser Gly Thr Lys Leu Glu Ile Lys Arg Ala Gly Ser Thr
            100                 105                 110

Ser Gly Gly Gly Ser Gly Gly Gly Ser Gly Gly Gly Gly Ser Ser Glu
        115                 120                 125

Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Lys Pro Gly Gly Ser
    130                 135                 140

Leu Lys Leu Ser Cys Ala Ala Ser Gly Phe Lys Phe Ser Arg Tyr Ala
145                 150                 155                 160

Met Ser Trp Val Arg Gln Ala Pro Gly Lys Arg Leu Glu Trp Val Ala
                165                 170                 175

Thr Ile Ser Ser Gly Gly Ser Tyr Ile Tyr Tyr Pro Asp Ser Val Lys
            180                 185                 190

Gly Arg Phe Thr Ile Ser Arg Asp Asn Val Lys Asn Thr Leu Tyr Leu
        195                 200                 205

Gln Met Ser Ser Leu Arg Ser Glu Asp Thr Ala Met Tyr Tyr Cys Ala
    210                 215                 220

Arg Arg Asp Tyr Asp Leu Asp Tyr Phe Asp Ser Trp Gly Gln Gly Thr
225                 230                 235                 240

Leu Val Thr Val Ser Ser Glu Ser Lys Tyr Gly Pro Pro Cys Pro Pro
                245                 250                 255

Cys Pro Ala Pro Glu Phe Glu Gly Gly Pro Ser Val Phe Leu Phe Pro
            260                 265                 270
```

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```
Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr
        275                 280                 285

Cys Val Val Val Asp Val Ser Gln Glu Asp Pro Glu Val Gln Phe Asn
    290                 295                 300

Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg
305                 310                 315                 320

Glu Glu Gln Phe Gln Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val
                325                 330                 335

Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser
            340                 345                 350

Asn Lys Gly Leu Pro Ser Ser Ile Glu Lys Thr Ile Ser Lys Ala Lys
        355                 360                 365

Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Gln Glu
    370                 375                 380

Glu Met Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe
385                 390                 395                 400

Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu
                405                 410                 415

Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe
            420                 425                 430

Phe Leu Tyr Ser Arg Leu Thr Val Asp Lys Ser Arg Trp Gln Glu Gly
        435                 440                 445

Asn Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr
    450                 455                 460

Thr Gln Lys Ser Leu Ser Leu Ser Leu Gly Lys Met Ala Leu Ile Val
465                 470                 475                 480

Leu Gly Gly Val Ala Gly Leu Leu Leu Phe Ile Gly Leu Gly Ile Phe
                485                 490                 495

Phe Lys Arg Gly Arg Lys Lys Leu Leu Tyr Ile Phe Lys Gln Pro Phe
            500                 505                 510

Met Arg Pro Val Gln Thr Thr Gln Glu Glu Asp Gly Cys Ser Cys Arg
        515                 520                 525

Phe Pro Glu Glu Glu Glu Gly Gly Cys Glu Leu Gly Gly Gly Arg Val
    530                 535                 540

Lys Phe Ser Arg Ser Ala Asp Ala Pro Ala Tyr Gln Gln Gly Gln Asn
545                 550                 555                 560

Gln Leu Tyr Asn Glu Leu Asn Leu Gly Arg Arg Glu Glu Tyr Asp Val
                565                 570                 575

Leu Asp Lys Arg Arg Gly Arg Asp Pro Glu Met Gly Gly Lys Pro Arg
            580                 585                 590

Arg Lys Asn Pro Gln Glu Gly Leu Tyr Asn Glu Leu Gln Lys Asp Lys
        595                 600                 605

Met Ala Glu Ala Tyr Ser Glu Ile Gly Met Lys Gly Glu Arg Arg Arg
    610                 615                 620

Gly Lys Gly His Asp Gly Leu Tyr Gln Gly Leu Ser Thr Ala Thr Lys
625                 630                 635                 640

Asp Thr Tyr Asp Ala Leu His Met Gln Ala Leu Pro Pro Arg
                645                 650


<210> SEQ ID NO 90
<211> LENGTH: 676
<212> TYPE: PRT
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<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic polypeptide"

<400> SEQUENCE: 90

Met Leu Leu Leu Val Thr Ser Leu Leu Leu Cys Glu Leu Pro His Pro
1 5 10 15

Ala Phe Leu Leu Ile Pro Asp Ile Gln Met Thr Gln Ser Pro Ser Ser
20 25 30

Leu Ser Ala Ser Val Gly Asp Arg Val Thr Ile Thr Cys Lys Ala Ser
35 40 45

Arg Asp Ile Arg Ser Tyr Leu Thr Trp Tyr Gln Gln Lys Pro Gly Lys
50 55 60

Ala Pro Lys Thr Leu Ile Tyr Tyr Ala Thr Ser Leu Ala Asp Gly Val
65 70 75 80

Pro Ser Arg Phe Ser Gly Ser Gly Ser Gly Gln Asp Tyr Ser Leu Thr
85 90 95

Ile Ser Ser Leu Glu Ser Asp Asp Thr Ala Thr Tyr Tyr Cys Leu Gln
100 105 110

His Gly Glu Ser Pro Phe Thr Phe Gly Ser Gly Thr Lys Leu Glu Ile
115 120 125

Lys Arg Ala Gly Ser Thr Ser Gly Gly Gly Ser Gly Gly Gly Ser Gly
130 135 140

Gly Gly Gly Ser Ser Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu
145 150 155 160

Val Lys Pro Gly Gly Ser Leu Lys Leu Ser Cys Ala Ala Ser Gly Phe
165 170 175

Lys Phe Ser Arg Tyr Ala Met Ser Trp Val Arg Gln Ala Pro Gly Lys
180 185 190

Arg Leu Glu Trp Val Ala Thr Ile Ser Ser Gly Gly Ser Tyr Ile Tyr
195 200 205

Tyr Pro Asp Ser Val Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Val
210 215 220

Lys Asn Thr Leu Tyr Leu Gln Met Ser Ser Leu Arg Ser Glu Asp Thr
225 230 235 240

Ala Met Tyr Tyr Cys Ala Arg Arg Asp Tyr Asp Leu Asp Tyr Phe Asp
245 250 255

Ser Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser Glu Ser Lys Tyr
260 265 270

Gly Pro Pro Cys Pro Pro Cys Pro Ala Pro Glu Phe Glu Gly Gly Pro
275 280 285

Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser
290 295 300

Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser Gln Glu Asp
305 310 315 320

Pro Glu Val Gln Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn
325 330 335

Ala Lys Thr Lys Pro Arg Glu Glu Gln Phe Gln Ser Thr Tyr Arg Val
340 345 350

Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu
355 360 365

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Tyr Lys Cys Lys Val Ser Asn Lys Gly Leu Pro Ser Ser Ile Glu Lys
    370                 375                 380

Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr
385                 390                 395                 400

Leu Pro Pro Ser Gln Glu Glu Met Thr Lys Asn Gln Val Ser Leu Thr
                405                 410                 415

Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu
            420                 425                 430

Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu
        435                 440                 445

Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Arg Leu Thr Val Asp Lys
    450                 455                 460

Ser Arg Trp Gln Glu Gly Asn Val Phe Ser Cys Ser Val Met His Glu
465                 470                 475                 480

Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Leu Gly
                485                 490                 495

Lys Met Ala Leu Ile Val Leu Gly Gly Val Ala Gly Leu Leu Leu Phe
            500                 505                 510

Ile Gly Leu Gly Ile Phe Phe Lys Arg Gly Arg Lys Lys Leu Leu Tyr
        515                 520                 525

Ile Phe Lys Gln Pro Phe Met Arg Pro Val Gln Thr Thr Gln Glu Glu
    530                 535                 540

Asp Gly Cys Ser Cys Arg Phe Pro Glu Glu Glu Glu Gly Gly Cys Glu
545                 550                 555                 560

Leu Gly Gly Gly Arg Val Lys Phe Ser Arg Ser Ala Asp Ala Pro Ala
                565                 570                 575

Tyr Gln Gln Gly Gln Asn Gln Leu Tyr Asn Glu Leu Asn Leu Gly Arg
            580                 585                 590

Arg Glu Glu Tyr Asp Val Leu Asp Lys Arg Arg Gly Arg Asp Pro Glu
        595                 600                 605

Met Gly Gly Lys Pro Arg Arg Lys Asn Pro Gln Glu Gly Leu Tyr Asn
    610                 615                 620

Glu Leu Gln Lys Asp Lys Met Ala Glu Ala Tyr Ser Glu Ile Gly Met
625                 630                 635                 640

Lys Gly Glu Arg Arg Arg Gly Lys Gly His Asp Gly Leu Tyr Gln Gly
                645                 650                 655

Leu Ser Thr Ala Thr Lys Asp Thr Tyr Asp Ala Leu His Met Gln Ala
            660                 665                 670

Leu Pro Pro Arg
        675


<210> SEQ ID NO 91
<211> LENGTH: 888
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
      Synthetic polypeptide"

<400> SEQUENCE: 91

Met Leu Leu Leu Val Thr Ser Leu Leu Leu Cys Glu Leu Pro His Pro
1               5                   10                  15
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Ala Phe Leu Leu Ile Pro Gly Pro Val Pro Pro Ser Thr Ala Leu Arg
            20                  25                  30

Tyr Leu Ile Glu Glu Leu Val Asn Ile Thr Gln Asn Gln Lys Ala Pro
        35                  40                  45

Leu Cys Asn Gly Ser Met Val Trp Ser Ile Asn Leu Thr Ala Gly Met
    50                  55                  60

Tyr Cys Ala Ala Leu Glu Ser Leu Ile Asn Val Ser Gly Cys Ser Ala
65                  70                  75                  80

Ile Glu Lys Thr Gln Arg Met Leu Ser Gly Phe Cys Pro His Lys Val
                85                  90                  95

Ser Ala Gly Gln Phe Ser Ser Leu His Val Arg Asp Thr Lys Ile Glu
            100                 105                 110

Val Ala Gln Phe Val Lys Asp Leu Leu Leu His Leu Lys Lys Leu Phe
        115                 120                 125

Arg Glu Gly Arg Phe Asn Glu Ser Lys Tyr Gly Pro Pro Cys Pro Pro
    130                 135                 140

Cys Pro Ala Pro Glu Phe Glu Gly Gly Pro Ser Val Phe Leu Phe Pro
145                 150                 155                 160

Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr
                165                 170                 175

Cys Val Val Val Asp Val Ser Gln Glu Asp Pro Glu Val Gln Phe Asn
            180                 185                 190

Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg
        195                 200                 205

Glu Glu Gln Phe Gln Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val
    210                 215                 220

Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser
225                 230                 235                 240

Asn Lys Gly Leu Pro Ser Ser Ile Glu Lys Thr Ile Ser Lys Ala Lys
                245                 250                 255

Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Gln Glu
            260                 265                 270

Glu Met Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe
        275                 280                 285

Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu
    290                 295                 300

Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe
305                 310                 315                 320

Phe Leu Tyr Ser Arg Leu Thr Val Asp Lys Ser Arg Trp Gln Glu Gly
                325                 330                 335

Asn Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr
            340                 345                 350

Thr Gln Lys Ser Leu Ser Leu Ser Leu Gly Lys Met Ala Leu Ile Val
        355                 360                 365

Leu Gly Gly Val Ala Gly Leu Leu Leu Phe Ile Gly Leu Gly Ile Phe
    370                 375                 380

Phe Ala Val Ser Leu Ser Lys Met Leu Lys Lys Arg Ser Pro Leu Thr
385                 390                 395                 400

Thr Gly Val Tyr Val Lys Met Pro Pro Thr Glu Pro Glu Cys Glu Lys
                405                 410                 415

Gln Phe Gln Pro Tyr Phe Ile Pro Ile Asn Gly Gly Gly Arg Val Lys
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            420                 425                 430

Phe Ser Arg Ser Ala Asp Ala Pro Ala Tyr Gln Gln Gly Gln Asn Gln
        435                 440                 445

Leu Tyr Asn Glu Leu Asn Leu Gly Arg Arg Glu Glu Tyr Asp Val Leu
    450                 455                 460

Asp Lys Arg Arg Gly Arg Asp Pro Glu Met Gly Gly Lys Pro Arg Arg
465                 470                 475                 480

Lys Asn Pro Gln Glu Gly Leu Tyr Asn Glu Leu Gln Lys Asp Lys Met
                485                 490                 495

Ala Glu Ala Tyr Ser Glu Ile Gly Met Lys Gly Glu Arg Arg Arg Gly
            500                 505                 510

Lys Gly His Asp Gly Leu Tyr Gln Gly Leu Ser Thr Ala Thr Lys Asp
        515                 520                 525

Thr Tyr Asp Ala Leu His Met Gln Ala Leu Pro Pro Arg Leu Glu Gly
    530                 535                 540

Gly Gly Glu Gly Arg Gly Ser Leu Leu Thr Cys Gly Asp Val Glu Glu
545                 550                 555                 560

Asn Pro Gly Pro Arg Met Pro Pro Pro Arg Leu Leu Phe Phe Leu Leu
                565                 570                 575

Phe Leu Thr Pro Met Glu Val Arg Pro Glu Glu Pro Leu Val Val Lys
            580                 585                 590

Val Glu Glu Gly Asp Asn Ala Val Leu Gln Cys Leu Lys Gly Thr Ser
        595                 600                 605

Asp Gly Pro Thr Gln Gln Leu Thr Trp Ser Arg Glu Ser Pro Leu Lys
    610                 615                 620

Pro Phe Leu Lys Leu Ser Leu Gly Leu Pro Gly Leu Gly Ile His Met
625                 630                 635                 640

Arg Pro Leu Ala Ile Trp Leu Phe Ile Phe Asn Val Ser Gln Gln Met
                645                 650                 655

Gly Gly Phe Tyr Leu Cys Gln Pro Gly Pro Pro Ser Glu Lys Ala Trp
            660                 665                 670

Gln Pro Gly Trp Thr Val Asn Val Glu Gly Ser Gly Glu Leu Phe Arg
        675                 680                 685

Trp Asn Val Ser Asp Leu Gly Gly Leu Gly Cys Gly Leu Lys Asn Arg
    690                 695                 700

Ser Ser Glu Gly Pro Ser Ser Pro Ser Gly Lys Leu Met Ser Pro Lys
705                 710                 715                 720

Leu Tyr Val Trp Ala Lys Asp Arg Pro Glu Ile Trp Glu Gly Glu Pro
                725                 730                 735

Pro Cys Val Pro Pro Arg Asp Ser Leu Asn Gln Ser Leu Ser Gln Asp
            740                 745                 750

Leu Thr Met Ala Pro Gly Ser Thr Leu Trp Leu Ser Cys Gly Val Pro
        755                 760                 765

Pro Asp Ser Val Ser Arg Gly Pro Leu Ser Trp Thr His Val His Pro
    770                 775                 780

Lys Gly Pro Lys Ser Leu Leu Ser Leu Glu Leu Lys Asp Asp Arg Pro
785                 790                 795                 800

Ala Arg Asp Met Trp Val Met Glu Thr Gly Leu Leu Leu Pro Arg Ala
                805                 810                 815

Thr Ala Gln Asp Ala Gly Lys Tyr Tyr Cys His Arg Gly Asn Leu Thr
            820                 825                 830
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```
Met Ser Phe His Leu Glu Ile Thr Ala Arg Pro Val Leu Trp His Trp
        835                 840                 845

Leu Leu Arg Thr Gly Gly Trp Lys Val Ser Ala Val Thr Leu Ala Tyr
    850                 855                 860

Leu Ile Phe Cys Leu Cys Ser Leu Val Gly Ile Leu His Leu Gln Arg
865                 870                 875                 880

Ala Leu Val Leu Arg Arg Lys Arg
                885


<210> SEQ ID NO 92
<211> LENGTH: 519
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
      Synthetic polypeptide"

<400> SEQUENCE: 92

Gly Pro Val Pro Pro Ser Thr Ala Leu Arg Tyr Leu Ile Glu Glu Leu
1               5                   10                  15

Val Asn Ile Thr Gln Asn Gln Lys Ala Pro Leu Cys Asn Gly Ser Met
            20                  25                  30

Val Trp Ser Ile Asn Leu Thr Ala Gly Met Tyr Cys Ala Ala Leu Glu
        35                  40                  45

Ser Leu Ile Asn Val Ser Gly Cys Ser Ala Ile Glu Lys Thr Gln Arg
    50                  55                  60

Met Leu Ser Gly Phe Cys Pro His Lys Val Ser Ala Gly Gln Phe Ser
65                  70                  75                  80

Ser Leu His Val Arg Asp Thr Lys Ile Glu Val Ala Gln Phe Val Lys
                85                  90                  95

Asp Leu Leu Leu His Leu Lys Lys Leu Phe Arg Glu Gly Arg Phe Asn
            100                 105                 110

Glu Ser Lys Tyr Gly Pro Pro Cys Pro Pro Cys Pro Ala Pro Glu Phe
        115                 120                 125

Glu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr
    130                 135                 140

Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val
145                 150                 155                 160

Ser Gln Glu Asp Pro Glu Val Gln Phe Asn Trp Tyr Val Asp Gly Val
                165                 170                 175

Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Phe Gln Ser
            180                 185                 190

Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu
        195                 200                 205

Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Gly Leu Pro Ser
    210                 215                 220

Ser Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro
225                 230                 235                 240

Gln Val Tyr Thr Leu Pro Pro Ser Gln Glu Glu Met Thr Lys Asn Gln
                245                 250                 255

Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala
            260                 265                 270
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```
Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr
        275                 280                 285

Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Arg Leu
    290                 295                 300

Thr Val Asp Lys Ser Arg Trp Gln Glu Gly Asn Val Phe Ser Cys Ser
305                 310                 315                 320

Val Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser
                325                 330                 335

Leu Ser Leu Gly Lys Met Ala Leu Ile Val Leu Gly Gly Val Ala Gly
            340                 345                 350

Leu Leu Leu Phe Ile Gly Leu Gly Ile Phe Phe Ala Val Ser Leu Ser
        355                 360                 365

Lys Met Leu Lys Lys Arg Ser Pro Leu Thr Thr Gly Val Tyr Val Lys
    370                 375                 380

Met Pro Pro Thr Glu Pro Glu Cys Glu Lys Gln Phe Gln Pro Tyr Phe
385                 390                 395                 400

Ile Pro Ile Asn Gly Gly Gly Arg Val Lys Phe Ser Arg Ser Ala Asp
                405                 410                 415

Ala Pro Ala Tyr Gln Gln Gly Gln Asn Gln Leu Tyr Asn Glu Leu Asn
            420                 425                 430

Leu Gly Arg Arg Glu Glu Tyr Asp Val Leu Asp Lys Arg Arg Gly Arg
        435                 440                 445

Asp Pro Glu Met Gly Gly Lys Pro Arg Arg Lys Asn Pro Gln Glu Gly
    450                 455                 460

Leu Tyr Asn Glu Leu Gln Lys Asp Lys Met Ala Glu Ala Tyr Ser Glu
465                 470                 475                 480

Ile Gly Met Lys Gly Glu Arg Arg Arg Gly Lys Gly His Asp Gly Leu
                485                 490                 495

Tyr Gln Gly Leu Ser Thr Ala Thr Lys Asp Thr Tyr Asp Ala Leu His
            500                 505                 510

Met Gln Ala Leu Pro Pro Arg
        515


<210> SEQ ID NO 93
<211> LENGTH: 1023
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
      Synthetic polypeptide"

<400> SEQUENCE: 93

Met Leu Leu Leu Val Thr Ser Leu Leu Leu Cys Glu Leu Pro His Pro
1               5                   10                  15

Ala Phe Leu Leu Ile Pro Glu Val Gln Leu Val Glu Ser Gly Gly Gly
            20                  25                  30

Leu Val Lys Pro Gly Gly Ser Leu Lys Leu Ser Cys Ala Ala Ser Gly
        35                  40                  45

Phe Lys Phe Ser Arg Tyr Ala Met Ser Trp Val Arg Gln Ala Pro Gly
    50                  55                  60

Lys Arg Leu Glu Trp Val Ala Thr Ile Ser Ser Gly Gly Ser Tyr Ile
65                  70                  75                  80

Tyr Tyr Pro Asp Ser Val Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn
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                85                  90                  95

Val Lys Asn Thr Leu Tyr Leu Gln Met Ser Ser Leu Arg Ser Glu Asp
            100                 105                 110

Thr Ala Met Tyr Tyr Cys Ala Arg Arg Asp Tyr Asp Leu Asp Tyr Phe
        115                 120                 125

Asp Ser Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser Gly Ser Thr
    130                 135                 140

Ser Gly Gly Gly Ser Gly Gly Gly Ser Gly Gly Gly Gly Ser Ser Asp
145                 150                 155                 160

Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly Asp
                165                 170                 175

Arg Val Thr Ile Thr Cys Lys Ala Ser Arg Asp Ile Arg Ser Tyr Leu
            180                 185                 190

Thr Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Thr Leu Ile Tyr
        195                 200                 205

Tyr Ala Thr Ser Leu Ala Asp Gly Val Pro Ser Arg Phe Ser Gly Ser
    210                 215                 220

Gly Ser Gly Gln Asp Tyr Ser Leu Thr Ile Ser Ser Leu Glu Ser Asp
225                 230                 235                 240

Asp Thr Ala Thr Tyr Tyr Cys Leu Gln His Gly Glu Ser Pro Phe Thr
                245                 250                 255

Phe Gly Ser Gly Thr Lys Leu Glu Ile Lys Arg Ala Glu Ser Lys Tyr
            260                 265                 270

Gly Pro Pro Cys Pro Pro Cys Pro Ala Pro Glu Phe Glu Gly Gly Pro
        275                 280                 285

Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser
    290                 295                 300

Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser Gln Glu Asp
305                 310                 315                 320

Pro Glu Val Gln Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn
                325                 330                 335

Ala Lys Thr Lys Pro Arg Glu Glu Gln Phe Gln Ser Thr Tyr Arg Val
            340                 345                 350

Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu
        355                 360                 365

Tyr Lys Cys Lys Val Ser Asn Lys Gly Leu Pro Ser Ser Ile Glu Lys
    370                 375                 380

Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr
385                 390                 395                 400

Leu Pro Pro Ser Gln Glu Glu Met Thr Lys Asn Gln Val Ser Leu Thr
                405                 410                 415

Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu
            420                 425                 430

Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu
        435                 440                 445

Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Arg Leu Thr Val Asp Lys
    450                 455                 460

Ser Arg Trp Gln Glu Gly Asn Val Phe Ser Cys Ser Val Met His Glu
465                 470                 475                 480

Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Leu Gly
                485                 490                 495
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```
Lys Met Ala Leu Ile Val Leu Gly Gly Val Ala Gly Leu Leu Leu Phe
            500                 505                 510

Ile Gly Leu Gly Ile Phe Phe Lys Arg Gly Arg Lys Lys Leu Leu Tyr
        515                 520                 525

Ile Phe Lys Gln Pro Phe Met Arg Pro Val Gln Thr Thr Gln Glu Glu
    530                 535                 540

Asp Gly Cys Ser Cys Arg Phe Pro Glu Glu Glu Glu Gly Gly Cys Glu
545                 550                 555                 560

Leu Gly Gly Gly Arg Val Lys Phe Ser Arg Ser Ala Asp Ala Pro Ala
                565                 570                 575

Tyr Gln Gln Gly Gln Asn Gln Leu Tyr Asn Glu Leu Asn Leu Gly Arg
            580                 585                 590

Arg Glu Glu Tyr Asp Val Leu Asp Lys Arg Arg Gly Arg Asp Pro Glu
        595                 600                 605

Met Gly Gly Lys Pro Arg Arg Lys Asn Pro Gln Glu Gly Leu Tyr Asn
    610                 615                 620

Glu Leu Gln Lys Asp Lys Met Ala Glu Ala Tyr Ser Glu Ile Gly Met
625                 630                 635                 640

Lys Gly Glu Arg Arg Arg Gly Lys Gly His Asp Gly Leu Tyr Gln Gly
                645                 650                 655

Leu Ser Thr Ala Thr Lys Asp Thr Tyr Asp Ala Leu His Met Gln Ala
            660                 665                 670

Leu Pro Pro Arg Leu Glu Gly Gly Gly Glu Gly Arg Gly Ser Leu Leu
        675                 680                 685

Thr Cys Gly Asp Val Glu Glu Asn Pro Gly Pro Arg Met Pro Pro Pro
    690                 695                 700

Arg Leu Leu Phe Phe Leu Leu Phe Leu Thr Pro Met Glu Val Arg Pro
705                 710                 715                 720

Glu Glu Pro Leu Val Val Lys Val Glu Glu Gly Asp Asn Ala Val Leu
                725                 730                 735

Gln Cys Leu Lys Gly Thr Ser Asp Gly Pro Thr Gln Gln Leu Thr Trp
            740                 745                 750

Ser Arg Glu Ser Pro Leu Lys Pro Phe Leu Lys Leu Ser Leu Gly Leu
        755                 760                 765

Pro Gly Leu Gly Ile His Met Arg Pro Leu Ala Ile Trp Leu Phe Ile
    770                 775                 780

Phe Asn Val Ser Gln Gln Met Gly Gly Phe Tyr Leu Cys Gln Pro Gly
785                 790                 795                 800

Pro Pro Ser Glu Lys Ala Trp Gln Pro Gly Trp Thr Val Asn Val Glu
                805                 810                 815

Gly Ser Gly Glu Leu Phe Arg Trp Asn Val Ser Asp Leu Gly Gly Leu
            820                 825                 830

Gly Cys Gly Leu Lys Asn Arg Ser Ser Glu Gly Pro Ser Ser Pro Ser
        835                 840                 845

Gly Lys Leu Met Ser Pro Lys Leu Tyr Val Trp Ala Lys Asp Arg Pro
    850                 855                 860

Glu Ile Trp Glu Gly Glu Pro Pro Cys Val Pro Pro Arg Asp Ser Leu
865                 870                 875                 880

Asn Gln Ser Leu Ser Gln Asp Leu Thr Met Ala Pro Gly Ser Thr Leu
                885                 890                 895
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```
Trp Leu Ser Cys Gly Val Pro Pro Asp Ser Val Ser Arg Gly Pro Leu
            900                 905                 910

Ser Trp Thr His Val His Pro Lys Gly Pro Lys Ser Leu Leu Ser Leu
        915                 920                 925

Glu Leu Lys Asp Asp Arg Pro Ala Arg Asp Met Trp Val Met Glu Thr
    930                 935                 940

Gly Leu Leu Leu Pro Arg Ala Thr Ala Gln Asp Ala Gly Lys Tyr Tyr
945                 950                 955                 960

Cys His Arg Gly Asn Leu Thr Met Ser Phe His Leu Glu Ile Thr Ala
                965                 970                 975

Arg Pro Val Leu Trp His Trp Leu Leu Arg Thr Gly Gly Trp Lys Val
            980                 985                 990

Ser Ala Val Thr Leu Ala Tyr Leu  Ile Phe Cys Leu Cys  Ser Leu Val
        995                 1000                1005

Gly Ile  Leu His Leu Gln Arg  Ala Leu Val Leu Arg  Arg Lys Arg
    1010                1015                1020


<210> SEQ ID NO 94
<211> LENGTH: 654
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
      Synthetic polypeptide"

<400> SEQUENCE: 94

Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Lys Pro Gly Gly
1               5                   10                  15

Ser Leu Lys Leu Ser Cys Ala Ala Ser Gly Phe Lys Phe Ser Arg Tyr
            20                  25                  30

Ala Met Ser Trp Val Arg Gln Ala Pro Gly Lys Arg Leu Glu Trp Val
        35                  40                  45

Ala Thr Ile Ser Ser Gly Gly Ser Tyr Ile Tyr Tyr Pro Asp Ser Val
    50                  55                  60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Val Lys Asn Thr Leu Tyr
65                  70                  75                  80

Leu Gln Met Ser Ser Leu Arg Ser Glu Asp Thr Ala Met Tyr Tyr Cys
                85                  90                  95

Ala Arg Arg Asp Tyr Asp Leu Asp Tyr Phe Asp Ser Trp Gly Gln Gly
            100                 105                 110

Thr Leu Val Thr Val Ser Ser Gly Ser Thr Ser Gly Gly Gly Ser Gly
        115                 120                 125

Gly Gly Ser Gly Gly Gly Gly Ser Ser Asp Ile Gln Met Thr Gln Ser
    130                 135                 140

Pro Ser Ser Leu Ser Ala Ser Val Gly Asp Arg Val Thr Ile Thr Cys
145                 150                 155                 160

Lys Ala Ser Arg Asp Ile Arg Ser Tyr Leu Thr Trp Tyr Gln Gln Lys
                165                 170                 175

Pro Gly Lys Ala Pro Lys Thr Leu Ile Tyr Tyr Ala Thr Ser Leu Ala
            180                 185                 190

Asp Gly Val Pro Ser Arg Phe Ser Gly Ser Gly Ser Gly Gln Asp Tyr
        195                 200                 205

Ser Leu Thr Ile Ser Ser Leu Glu Ser Asp Asp Thr Ala Thr Tyr Tyr
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    210                 215                 220

Cys Leu Gln His Gly Glu Ser Pro Phe Thr Phe Gly Ser Gly Thr Lys
225                 230                 235                 240

Leu Glu Ile Lys Arg Ala Glu Ser Lys Tyr Gly Pro Pro Cys Pro Pro
                245                 250                 255

Cys Pro Ala Pro Glu Phe Glu Gly Gly Pro Ser Val Phe Leu Phe Pro
            260                 265                 270

Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr
        275                 280                 285

Cys Val Val Val Asp Val Ser Gln Glu Asp Pro Glu Val Gln Phe Asn
    290                 295                 300

Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg
305                 310                 315                 320

Glu Glu Gln Phe Gln Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val
                325                 330                 335

Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser
            340                 345                 350

Asn Lys Gly Leu Pro Ser Ser Ile Glu Lys Thr Ile Ser Lys Ala Lys
        355                 360                 365

Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Gln Glu
    370                 375                 380

Glu Met Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe
385                 390                 395                 400

Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu
                405                 410                 415

Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe
            420                 425                 430

Phe Leu Tyr Ser Arg Leu Thr Val Asp Lys Ser Arg Trp Gln Glu Gly
        435                 440                 445

Asn Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr
    450                 455                 460

Thr Gln Lys Ser Leu Ser Leu Ser Leu Gly Lys Met Ala Leu Ile Val
465                 470                 475                 480

Leu Gly Gly Val Ala Gly Leu Leu Leu Phe Ile Gly Leu Gly Ile Phe
                485                 490                 495

Phe Lys Arg Gly Arg Lys Lys Leu Leu Tyr Ile Phe Lys Gln Pro Phe
            500                 505                 510

Met Arg Pro Val Gln Thr Thr Gln Glu Glu Asp Gly Cys Ser Cys Arg
        515                 520                 525

Phe Pro Glu Glu Glu Glu Gly Gly Cys Glu Leu Gly Gly Gly Arg Val
    530                 535                 540

Lys Phe Ser Arg Ser Ala Asp Ala Pro Ala Tyr Gln Gln Gly Gln Asn
545                 550                 555                 560

Gln Leu Tyr Asn Glu Leu Asn Leu Gly Arg Arg Glu Glu Tyr Asp Val
                565                 570                 575

Leu Asp Lys Arg Arg Gly Arg Asp Pro Glu Met Gly Gly Lys Pro Arg
            580                 585                 590

Arg Lys Asn Pro Gln Glu Gly Leu Tyr Asn Glu Leu Gln Lys Asp Lys
        595                 600                 605

Met Ala Glu Ala Tyr Ser Glu Ile Gly Met Lys Gly Glu Arg Arg Arg
    610                 615                 620
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Gly Lys Gly His Asp Gly Leu Tyr Gln Gly Leu Ser Thr Ala Thr Lys
625                 630                 635                 640

Asp Thr Tyr Asp Ala Leu His Met Gln Ala Leu Pro Pro Arg
                645                 650


<210> SEQ ID NO 95
<211> LENGTH: 1022
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
      Synthetic polypeptide"

<400> SEQUENCE: 95

Met Leu Leu Leu Val Thr Ser Leu Leu Leu Cys Glu Leu Pro His Pro
1               5                   10                  15

Ala Phe Leu Leu Ile Pro Glu Val Gln Leu Val Glu Ser Gly Gly Gly
            20                  25                  30

Leu Val Lys Pro Gly Gly Ser Leu Lys Leu Ser Cys Ala Ala Ser Gly
        35                  40                  45

Phe Lys Phe Ser Arg Tyr Ala Met Ser Trp Val Arg Gln Ala Pro Gly
    50                  55                  60

Lys Arg Leu Glu Trp Val Ala Thr Ile Ser Ser Gly Gly Ser Tyr Ile
65                  70                  75                  80

Tyr Tyr Pro Asp Ser Val Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn
                85                  90                  95

Val Lys Asn Thr Leu Tyr Leu Gln Met Ser Ser Leu Arg Ser Glu Asp
            100                 105                 110

Thr Ala Met Tyr Tyr Cys Ala Arg Arg Asp Tyr Asp Leu Asp Tyr Phe
        115                 120                 125

Asp Ser Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser Gly Ser Thr
    130                 135                 140

Ser Gly Gly Gly Ser Gly Gly Gly Ser Gly Gly Gly Gly Ser Ser Asp
145                 150                 155                 160

Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly Asp
                165                 170                 175

Arg Val Thr Ile Thr Cys Lys Ala Ser Arg Asp Ile Arg Ser Tyr Leu
            180                 185                 190

Thr Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Thr Leu Ile Tyr
        195                 200                 205

Tyr Ala Thr Ser Leu Ala Asp Gly Val Pro Ser Arg Phe Ser Gly Ser
    210                 215                 220

Gly Ser Gly Gln Asp Tyr Ser Leu Thr Ile Ser Ser Leu Glu Ser Asp
225                 230                 235                 240

Asp Thr Ala Thr Tyr Tyr Cys Leu Gln His Gly Glu Ser Pro Phe Thr
                245                 250                 255

Phe Gly Ser Gly Thr Lys Leu Glu Ile Lys Arg Ala Glu Ser Lys Tyr
            260                 265                 270

Gly Pro Pro Cys Pro Pro Cys Pro Ala Pro Glu Phe Glu Gly Gly Pro
        275                 280                 285

Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser
    290                 295                 300
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Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser Gln Glu Asp
305                 310                 315                 320

Pro Glu Val Gln Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn
                325                 330                 335

Ala Lys Thr Lys Pro Arg Glu Glu Gln Phe Gln Ser Thr Tyr Arg Val
            340                 345                 350

Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu
        355                 360                 365

Tyr Lys Cys Lys Val Ser Asn Lys Gly Leu Pro Ser Ser Ile Glu Lys
    370                 375                 380

Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr
385                 390                 395                 400

Leu Pro Pro Ser Gln Glu Glu Met Thr Lys Asn Gln Val Ser Leu Thr
                405                 410                 415

Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu
            420                 425                 430

Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu
        435                 440                 445

Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Arg Leu Thr Val Asp Lys
    450                 455                 460

Ser Arg Trp Gln Glu Gly Asn Val Phe Ser Cys Ser Val Met His Glu
465                 470                 475                 480

Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Leu Gly
                485                 490                 495

Lys Met Ala Leu Ile Val Leu Gly Gly Val Ala Gly Leu Leu Leu Phe
            500                 505                 510

Ile Gly Leu Gly Ile Phe Phe Ala Val Ser Leu Ser Lys Met Leu Lys
        515                 520                 525

Lys Arg Ser Pro Leu Thr Thr Gly Val Tyr Val Lys Met Pro Pro Thr
    530                 535                 540

Glu Pro Glu Cys Glu Lys Gln Phe Gln Pro Tyr Phe Ile Pro Ile Asn
545                 550                 555                 560

Gly Gly Gly Arg Val Lys Phe Ser Arg Ser Ala Asp Ala Pro Ala Tyr
                565                 570                 575

Gln Gln Gly Gln Asn Gln Leu Tyr Asn Glu Leu Asn Leu Gly Arg Arg
            580                 585                 590

Glu Glu Tyr Asp Val Leu Asp Lys Arg Arg Gly Arg Asp Pro Glu Met
        595                 600                 605

Gly Gly Lys Pro Arg Arg Lys Asn Pro Gln Glu Gly Leu Tyr Asn Glu
    610                 615                 620

Leu Gln Lys Asp Lys Met Ala Glu Ala Tyr Ser Glu Ile Gly Met Lys
625                 630                 635                 640

Gly Glu Arg Arg Arg Gly Lys Gly His Asp Gly Leu Tyr Gln Gly Leu
                645                 650                 655

Ser Thr Ala Thr Lys Asp Thr Tyr Asp Ala Leu His Met Gln Ala Leu
            660                 665                 670

Pro Pro Arg Leu Glu Gly Gly Gly Glu Gly Arg Gly Ser Leu Leu Thr
        675                 680                 685

Cys Gly Asp Val Glu Glu Asn Pro Gly Pro Arg Met Pro Pro Pro Arg
    690                 695                 700

Leu Leu Phe Phe Leu Leu Phe Leu Thr Pro Met Glu Val Arg Pro Glu
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705                 710                 715                 720

Glu Pro Leu Val Val Lys Val Glu Glu Gly Asp Asn Ala Val Leu Gln
                725                 730                 735

Cys Leu Lys Gly Thr Ser Asp Gly Pro Thr Gln Gln Leu Thr Trp Ser
            740                 745                 750

Arg Glu Ser Pro Leu Lys Pro Phe Leu Lys Leu Ser Leu Gly Leu Pro
        755                 760                 765

Gly Leu Gly Ile His Met Arg Pro Leu Ala Ile Trp Leu Phe Ile Phe
    770                 775                 780

Asn Val Ser Gln Gln Met Gly Gly Phe Tyr Leu Cys Gln Pro Gly Pro
785                 790                 795                 800

Pro Ser Glu Lys Ala Trp Gln Pro Gly Trp Thr Val Asn Val Glu Gly
                805                 810                 815

Ser Gly Glu Leu Phe Arg Trp Asn Val Ser Asp Leu Gly Gly Leu Gly
            820                 825                 830

Cys Gly Leu Lys Asn Arg Ser Ser Glu Gly Pro Ser Ser Pro Ser Gly
        835                 840                 845

Lys Leu Met Ser Pro Lys Leu Tyr Val Trp Ala Lys Asp Arg Pro Glu
    850                 855                 860

Ile Trp Glu Gly Glu Pro Pro Cys Val Pro Pro Arg Asp Ser Leu Asn
865                 870                 875                 880

Gln Ser Leu Ser Gln Asp Leu Thr Met Ala Pro Gly Ser Thr Leu Trp
                885                 890                 895

Leu Ser Cys Gly Val Pro Pro Asp Ser Val Ser Arg Gly Pro Leu Ser
            900                 905                 910

Trp Thr His Val His Pro Lys Gly Pro Lys Ser Leu Leu Ser Leu Glu
        915                 920                 925

Leu Lys Asp Asp Arg Pro Ala Arg Asp Met Trp Val Met Glu Thr Gly
    930                 935                 940

Leu Leu Leu Pro Arg Ala Thr Ala Gln Asp Ala Gly Lys Tyr Tyr Cys
945                 950                 955                 960

His Arg Gly Asn Leu Thr Met Ser Phe His Leu Glu Ile Thr Ala Arg
                965                 970                 975

Pro Val Leu Trp His Trp Leu Leu Arg Thr Gly Gly Trp Lys Val Ser
            980                 985                 990

Ala Val Thr Leu Ala Tyr Leu Ile  Phe Cys Leu Cys Ser  Leu Val Gly
        995                 1000                1005

Ile Leu  His Leu Gln Arg Ala  Leu Val Leu Arg Arg  Lys Arg
    1010                1015                1020


<210> SEQ ID NO 96
<211> LENGTH: 653
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
      Synthetic polypeptide"

<400> SEQUENCE: 96

Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Lys Pro Gly Gly
1               5                   10                  15

Ser Leu Lys Leu Ser Cys Ala Ala Ser Gly Phe Lys Phe Ser Arg Tyr
            20                  25                  30
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Ala Met Ser Trp Val Arg Gln Ala Pro Gly Lys Arg Leu Glu Trp Val
        35                  40                  45

Ala Thr Ile Ser Ser Gly Gly Ser Tyr Ile Tyr Tyr Pro Asp Ser Val
    50                  55                  60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Val Lys Asn Thr Leu Tyr
65                  70                  75                  80

Leu Gln Met Ser Ser Leu Arg Ser Glu Asp Thr Ala Met Tyr Tyr Cys
                85                  90                  95

Ala Arg Arg Asp Tyr Asp Leu Asp Tyr Phe Asp Ser Trp Gly Gln Gly
            100                 105                 110

Thr Leu Val Thr Val Ser Ser Gly Ser Thr Ser Gly Gly Gly Ser Gly
        115                 120                 125

Gly Gly Ser Gly Gly Gly Gly Ser Ser Asp Ile Gln Met Thr Gln Ser
    130                 135                 140

Pro Ser Ser Leu Ser Ala Ser Val Gly Asp Arg Val Thr Ile Thr Cys
145                 150                 155                 160

Lys Ala Ser Arg Asp Ile Arg Ser Tyr Leu Thr Trp Tyr Gln Gln Lys
                165                 170                 175

Pro Gly Lys Ala Pro Lys Thr Leu Ile Tyr Tyr Ala Thr Ser Leu Ala
            180                 185                 190

Asp Gly Val Pro Ser Arg Phe Ser Gly Ser Gly Ser Gly Gln Asp Tyr
        195                 200                 205

Ser Leu Thr Ile Ser Ser Leu Glu Ser Asp Asp Thr Ala Thr Tyr Tyr
    210                 215                 220

Cys Leu Gln His Gly Glu Ser Pro Phe Thr Phe Gly Ser Gly Thr Lys
225                 230                 235                 240

Leu Glu Ile Lys Arg Ala Glu Ser Lys Tyr Gly Pro Pro Cys Pro Pro
                245                 250                 255

Cys Pro Ala Pro Glu Phe Glu Gly Gly Pro Ser Val Phe Leu Phe Pro
            260                 265                 270

Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr
        275                 280                 285

Cys Val Val Val Asp Val Ser Gln Glu Asp Pro Glu Val Gln Phe Asn
    290                 295                 300

Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg
305                 310                 315                 320

Glu Glu Gln Phe Gln Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val
                325                 330                 335

Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser
            340                 345                 350

Asn Lys Gly Leu Pro Ser Ser Ile Glu Lys Thr Ile Ser Lys Ala Lys
        355                 360                 365

Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Gln Glu
    370                 375                 380

Glu Met Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe
385                 390                 395                 400

Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu
                405                 410                 415

Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe
            420                 425                 430
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Phe Leu Tyr Ser Arg Leu Thr Val Asp Lys Ser Arg Trp Gln Glu Gly
        435                 440                 445

Asn Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr
    450                 455                 460

Thr Gln Lys Ser Leu Ser Leu Ser Leu Gly Lys Met Ala Leu Ile Val
465                 470                 475                 480

Leu Gly Gly Val Ala Gly Leu Leu Leu Phe Ile Gly Leu Gly Ile Phe
                485                 490                 495

Phe Ala Val Ser Leu Ser Lys Met Leu Lys Lys Arg Ser Pro Leu Thr
            500                 505                 510

Thr Gly Val Tyr Val Lys Met Pro Pro Thr Glu Pro Glu Cys Glu Lys
        515                 520                 525

Gln Phe Gln Pro Tyr Phe Ile Pro Ile Asn Gly Gly Gly Arg Val Lys
    530                 535                 540

Phe Ser Arg Ser Ala Asp Ala Pro Ala Tyr Gln Gln Gly Gln Asn Gln
545                 550                 555                 560

Leu Tyr Asn Glu Leu Asn Leu Gly Arg Arg Glu Glu Tyr Asp Val Leu
                565                 570                 575

Asp Lys Arg Arg Gly Arg Asp Pro Glu Met Gly Gly Lys Pro Arg Arg
            580                 585                 590

Lys Asn Pro Gln Glu Gly Leu Tyr Asn Glu Leu Gln Lys Asp Lys Met
        595                 600                 605

Ala Glu Ala Tyr Ser Glu Ile Gly Met Lys Gly Glu Arg Arg Arg Gly
    610                 615                 620

Lys Gly His Asp Gly Leu Tyr Gln Gly Leu Ser Thr Ala Thr Lys Asp
625                 630                 635                 640

Thr Tyr Asp Ala Leu His Met Gln Ala Leu Pro Pro Arg
                645                 650


<210> SEQ ID NO 97
<211> LENGTH: 1023
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
      Synthetic polypeptide"

<400> SEQUENCE: 97

Met Leu Leu Leu Val Thr Ser Leu Leu Leu Cys Glu Leu Pro His Pro
1               5                   10                  15

Ala Phe Leu Leu Ile Pro Glu Val Gln Leu Val Glu Ser Gly Gly Gly
            20                  25                  30

Leu Val Lys Pro Gly Gly Ser Leu Lys Leu Ser Cys Ala Ala Ser Gly
        35                  40                  45

Phe Lys Phe Ser Arg Tyr Ala Met Ser Trp Val Arg Gln Ala Pro Gly
    50                  55                  60

Lys Gly Leu Glu Trp Val Ala Thr Ile Ser Ser Gly Gly Ser Tyr Ile
65                  70                  75                  80

Tyr Tyr Pro Asp Ser Val Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn
                85                  90                  95

Val Lys Asn Thr Leu Tyr Leu Gln Met Ser Ser Leu Arg Ser Glu Asp
            100                 105                 110

Thr Ala Met Tyr Tyr Cys Ala Arg Arg Asp Tyr Asp Leu Asp Tyr Phe
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        115                 120                 125

Asp Ser Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser Gly Ser Thr
    130                 135                 140

Ser Gly Gly Gly Ser Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Asp
145                 150                 155                 160

Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly Asp
                165                 170                 175

Arg Val Thr Ile Thr Cys Lys Ala Ser Arg Asp Ile Arg Ser Tyr Leu
            180                 185                 190

Thr Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Thr Leu Ile Tyr
        195                 200                 205

Tyr Ala Thr Ser Leu Ala Asp Gly Val Pro Ser Arg Phe Ser Gly Ser
    210                 215                 220

Gly Ser Gly Gln Asp Tyr Ser Leu Thr Ile Ser Ser Leu Glu Ser Asp
225                 230                 235                 240

Asp Thr Ala Thr Tyr Tyr Cys Leu Gln His Gly Glu Ser Pro Phe Thr
                245                 250                 255

Phe Gly Ser Gly Thr Lys Met Glu Ile Lys Arg Ala Glu Ser Lys Tyr
            260                 265                 270

Gly Pro Pro Cys Pro Pro Cys Pro Ala Pro Glu Phe Glu Gly Gly Pro
        275                 280                 285

Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser
    290                 295                 300

Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser Gln Glu Asp
305                 310                 315                 320

Pro Glu Val Gln Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn
                325                 330                 335

Ala Lys Thr Lys Pro Arg Glu Glu Gln Phe Gln Ser Thr Tyr Arg Val
            340                 345                 350

Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu
        355                 360                 365

Tyr Lys Cys Lys Val Ser Asn Lys Gly Leu Pro Ser Ser Ile Glu Lys
    370                 375                 380

Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr
385                 390                 395                 400

Leu Pro Pro Ser Gln Glu Glu Met Thr Lys Asn Gln Val Ser Leu Thr
                405                 410                 415

Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu
            420                 425                 430

Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu
        435                 440                 445

Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Arg Leu Thr Val Asp Lys
    450                 455                 460

Ser Arg Trp Gln Glu Gly Asn Val Phe Ser Cys Ser Val Met His Glu
465                 470                 475                 480

Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Leu Gly
                485                 490                 495

Lys Met Ala Leu Ile Val Leu Gly Gly Val Ala Gly Leu Leu Leu Phe
            500                 505                 510

Ile Gly Leu Gly Ile Phe Phe Lys Arg Gly Arg Lys Lys Leu Leu Tyr
        515                 520                 525
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Ile Phe Lys Gln Pro Phe Met Arg Pro Val Gln Thr Thr Gln Glu Glu
    530                 535                 540

Asp Gly Cys Ser Cys Arg Phe Pro Glu Glu Glu Glu Gly Gly Cys Glu
545                 550                 555                 560

Leu Gly Gly Gly Arg Val Lys Phe Ser Arg Ser Ala Asp Ala Pro Ala
                565                 570                 575

Tyr Gln Gln Gly Gln Asn Gln Leu Tyr Asn Glu Leu Asn Leu Gly Arg
            580                 585                 590

Arg Glu Glu Tyr Asp Val Leu Asp Lys Arg Arg Gly Arg Asp Pro Glu
        595                 600                 605

Met Gly Gly Lys Pro Arg Arg Lys Asn Pro Gln Glu Gly Leu Tyr Asn
    610                 615                 620

Glu Leu Gln Lys Asp Lys Met Ala Glu Ala Tyr Ser Glu Ile Gly Met
625                 630                 635                 640

Lys Gly Glu Arg Arg Arg Gly Lys Gly His Asp Gly Leu Tyr Gln Gly
                645                 650                 655

Leu Ser Thr Ala Thr Lys Asp Thr Tyr Asp Ala Leu His Met Gln Ala
            660                 665                 670

Leu Pro Pro Arg Leu Glu Gly Gly Gly Glu Gly Arg Gly Ser Leu Leu
        675                 680                 685

Thr Cys Gly Asp Val Glu Glu Asn Pro Gly Pro Arg Met Pro Pro Pro
    690                 695                 700

Arg Leu Leu Phe Phe Leu Leu Phe Leu Thr Pro Met Glu Val Arg Pro
705                 710                 715                 720

Glu Glu Pro Leu Val Val Lys Val Glu Glu Gly Asp Asn Ala Val Leu
                725                 730                 735

Gln Cys Leu Lys Gly Thr Ser Asp Gly Pro Thr Gln Gln Leu Thr Trp
            740                 745                 750

Ser Arg Glu Ser Pro Leu Lys Pro Phe Leu Lys Leu Ser Leu Gly Leu
        755                 760                 765

Pro Gly Leu Gly Ile His Met Arg Pro Leu Ala Ile Trp Leu Phe Ile
    770                 775                 780

Phe Asn Val Ser Gln Gln Met Gly Gly Phe Tyr Leu Cys Gln Pro Gly
785                 790                 795                 800

Pro Pro Ser Glu Lys Ala Trp Gln Pro Gly Trp Thr Val Asn Val Glu
                805                 810                 815

Gly Ser Gly Glu Leu Phe Arg Trp Asn Val Ser Asp Leu Gly Gly Leu
            820                 825                 830

Gly Cys Gly Leu Lys Asn Arg Ser Ser Glu Gly Pro Ser Ser Pro Ser
        835                 840                 845

Gly Lys Leu Met Ser Pro Lys Leu Tyr Val Trp Ala Lys Asp Arg Pro
    850                 855                 860

Glu Ile Trp Glu Gly Glu Pro Pro Cys Val Pro Pro Arg Asp Ser Leu
865                 870                 875                 880

Asn Gln Ser Leu Ser Gln Asp Leu Thr Met Ala Pro Gly Ser Thr Leu
                885                 890                 895

Trp Leu Ser Cys Gly Val Pro Pro Asp Ser Val Ser Arg Gly Pro Leu
            900                 905                 910

Ser Trp Thr His Val His Pro Lys Gly Pro Lys Ser Leu Leu Ser Leu
        915                 920                 925
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```
Glu Leu Lys Asp Asp Arg Pro Ala Arg Asp Met Trp Val Met Glu Thr
    930                 935                 940

Gly Leu Leu Leu Pro Arg Ala Thr Ala Gln Asp Ala Gly Lys Tyr Tyr
945                 950                 955                 960

Cys His Arg Gly Asn Leu Thr Met Ser Phe His Leu Glu Ile Thr Ala
                965                 970                 975

Arg Pro Val Leu Trp His Trp Leu Leu Arg Thr Gly Gly Trp Lys Val
            980                 985                 990

Ser Ala Val Thr Leu Ala Tyr Leu  Ile Phe Cys Leu Cys  Ser Leu Val
        995                 1000                1005

Gly Ile  Leu His Leu Gln Arg  Ala Leu Val Leu Arg  Arg Lys Arg
    1010                1015                1020


<210> SEQ ID NO 98
<211> LENGTH: 654
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
      Synthetic polypeptide"

<400> SEQUENCE: 98

Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Lys Pro Gly Gly
1               5                   10                  15

Ser Leu Lys Leu Ser Cys Ala Ala Ser Gly Phe Lys Phe Ser Arg Tyr
            20                  25                  30

Ala Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
        35                  40                  45

Ala Thr Ile Ser Ser Gly Gly Ser Tyr Ile Tyr Tyr Pro Asp Ser Val
    50                  55                  60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Val Lys Asn Thr Leu Tyr
65                  70                  75                  80

Leu Gln Met Ser Ser Leu Arg Ser Glu Asp Thr Ala Met Tyr Tyr Cys
                85                  90                  95

Ala Arg Arg Asp Tyr Asp Leu Asp Tyr Phe Asp Ser Trp Gly Gln Gly
            100                 105                 110

Thr Leu Val Thr Val Ser Ser Gly Ser Thr Ser Gly Gly Gly Ser Gly
        115                 120                 125

Gly Gly Ser Gly Gly Gly Gly Ser Gly Asp Ile Gln Met Thr Gln Ser
    130                 135                 140

Pro Ser Ser Leu Ser Ala Ser Val Gly Asp Arg Val Thr Ile Thr Cys
145                 150                 155                 160

Lys Ala Ser Arg Asp Ile Arg Ser Tyr Leu Thr Trp Tyr Gln Gln Lys
                165                 170                 175

Pro Gly Lys Ala Pro Lys Thr Leu Ile Tyr Tyr Ala Thr Ser Leu Ala
            180                 185                 190

Asp Gly Val Pro Ser Arg Phe Ser Gly Ser Gly Ser Gly Gln Asp Tyr
        195                 200                 205

Ser Leu Thr Ile Ser Ser Leu Glu Ser Asp Asp Thr Ala Thr Tyr Tyr
    210                 215                 220

Cys Leu Gln His Gly Glu Ser Pro Phe Thr Phe Gly Ser Gly Thr Lys
225                 230                 235                 240

Met Glu Ile Lys Arg Ala Glu Ser Lys Tyr Gly Pro Pro Cys Pro Pro
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               245                 250                 255

Cys Pro Ala Pro Glu Phe Glu Gly Gly Pro Ser Val Phe Leu Phe Pro
            260                 265                 270

Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr
        275                 280                 285

Cys Val Val Val Asp Val Ser Gln Glu Asp Pro Glu Val Gln Phe Asn
    290                 295                 300

Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg
305                 310                 315                 320

Glu Glu Gln Phe Gln Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val
                325                 330                 335

Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser
            340                 345                 350

Asn Lys Gly Leu Pro Ser Ser Ile Glu Lys Thr Ile Ser Lys Ala Lys
        355                 360                 365

Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Gln Glu
    370                 375                 380

Glu Met Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe
385                 390                 395                 400

Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu
                405                 410                 415

Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe
            420                 425                 430

Phe Leu Tyr Ser Arg Leu Thr Val Asp Lys Ser Arg Trp Gln Glu Gly
        435                 440                 445

Asn Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr
    450                 455                 460

Thr Gln Lys Ser Leu Ser Leu Ser Leu Gly Lys Met Ala Leu Ile Val
465                 470                 475                 480

Leu Gly Gly Val Ala Gly Leu Leu Leu Phe Ile Gly Leu Gly Ile Phe
                485                 490                 495

Phe Lys Arg Gly Arg Lys Lys Leu Leu Tyr Ile Phe Lys Gln Pro Phe
            500                 505                 510

Met Arg Pro Val Gln Thr Thr Gln Glu Glu Asp Gly Cys Ser Cys Arg
        515                 520                 525

Phe Pro Glu Glu Glu Glu Gly Gly Cys Glu Leu Gly Gly Gly Arg Val
    530                 535                 540

Lys Phe Ser Arg Ser Ala Asp Ala Pro Ala Tyr Gln Gln Gly Gln Asn
545                 550                 555                 560

Gln Leu Tyr Asn Glu Leu Asn Leu Gly Arg Arg Glu Glu Tyr Asp Val
                565                 570                 575

Leu Asp Lys Arg Arg Gly Arg Asp Pro Glu Met Gly Gly Lys Pro Arg
            580                 585                 590

Arg Lys Asn Pro Gln Glu Gly Leu Tyr Asn Glu Leu Gln Lys Asp Lys
        595                 600                 605

Met Ala Glu Ala Tyr Ser Glu Ile Gly Met Lys Gly Glu Arg Arg Arg
    610                 615                 620

Gly Lys Gly His Asp Gly Leu Tyr Gln Gly Leu Ser Thr Ala Thr Lys
625                 630                 635                 640

Asp Thr Tyr Asp Ala Leu His Met Gln Ala Leu Pro Pro Arg
                645                 650
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<210> SEQ ID NO 99
<211> LENGTH: 1022
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic polypeptide"

<400> SEQUENCE: 99

Met Leu Leu Leu Val Thr Ser Leu Leu Leu Cys Glu Leu Pro His Pro
1 5 10 15

Ala Phe Leu Leu Ile Pro Glu Val Gln Leu Val Glu Ser Gly Gly Gly
20 25 30

Leu Val Lys Pro Gly Gly Ser Leu Lys Leu Ser Cys Ala Ala Ser Gly
35 40 45

Phe Lys Phe Ser Arg Tyr Ala Met Ser Trp Val Arg Gln Ala Pro Gly
50 55 60

Lys Gly Leu Glu Trp Val Ala Thr Ile Ser Ser Gly Gly Ser Tyr Ile
65 70 75 80

Tyr Tyr Pro Asp Ser Val Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn
85 90 95

Val Lys Asn Thr Leu Tyr Leu Gln Met Ser Ser Leu Arg Ser Glu Asp
100 105 110

Thr Ala Met Tyr Tyr Cys Ala Arg Arg Asp Tyr Asp Leu Asp Tyr Phe
115 120 125

Asp Ser Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser Gly Ser Thr
130 135 140

Ser Gly Gly Gly Ser Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Asp
145 150 155 160

Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly Asp
165 170 175

Arg Val Thr Ile Thr Cys Lys Ala Ser Arg Asp Ile Arg Ser Tyr Leu
180 185 190

Thr Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Thr Leu Ile Tyr
195 200 205

Tyr Ala Thr Ser Leu Ala Asp Gly Val Pro Ser Arg Phe Ser Gly Ser
210 215 220

Gly Ser Gly Gln Asp Tyr Ser Leu Thr Ile Ser Ser Leu Glu Ser Asp
225 230 235 240

Asp Thr Ala Thr Tyr Tyr Cys Leu Gln His Gly Glu Ser Pro Phe Thr
245 250 255

Phe Gly Ser Gly Thr Lys Met Glu Ile Lys Arg Ala Glu Ser Lys Tyr
260 265 270

Gly Pro Pro Cys Pro Pro Cys Pro Ala Pro Glu Phe Glu Gly Gly Pro
275 280 285

Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser
290 295 300

Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser Gln Glu Asp
305 310 315 320

Pro Glu Val Gln Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn
325 330 335

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Ala Lys Thr Lys Pro Arg Glu Glu Gln Phe Gln Ser Thr Tyr Arg Val
            340                 345                 350

Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu
        355                 360                 365

Tyr Lys Cys Lys Val Ser Asn Lys Gly Leu Pro Ser Ser Ile Glu Lys
    370                 375                 380

Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr
385                 390                 395                 400

Leu Pro Pro Ser Gln Glu Glu Met Thr Lys Asn Gln Val Ser Leu Thr
                405                 410                 415

Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu
            420                 425                 430

Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu
        435                 440                 445

Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Arg Leu Thr Val Asp Lys
    450                 455                 460

Ser Arg Trp Gln Glu Gly Asn Val Phe Ser Cys Ser Val Met His Glu
465                 470                 475                 480

Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Leu Gly
                485                 490                 495

Lys Met Ala Leu Ile Val Leu Gly Gly Val Ala Gly Leu Leu Leu Phe
            500                 505                 510

Ile Gly Leu Gly Ile Phe Phe Ala Val Ser Leu Ser Lys Met Leu Lys
        515                 520                 525

Lys Arg Ser Pro Leu Thr Thr Gly Val Tyr Val Lys Met Pro Pro Thr
    530                 535                 540

Glu Pro Glu Cys Glu Lys Gln Phe Gln Pro Tyr Phe Ile Pro Ile Asn
545                 550                 555                 560

Gly Gly Gly Arg Val Lys Phe Ser Arg Ser Ala Asp Ala Pro Ala Tyr
                565                 570                 575

Gln Gln Gly Gln Asn Gln Leu Tyr Asn Glu Leu Asn Leu Gly Arg Arg
            580                 585                 590

Glu Glu Tyr Asp Val Leu Asp Lys Arg Arg Gly Arg Asp Pro Glu Met
        595                 600                 605

Gly Gly Lys Pro Arg Arg Lys Asn Pro Gln Glu Gly Leu Tyr Asn Glu
    610                 615                 620

Leu Gln Lys Asp Lys Met Ala Glu Ala Tyr Ser Glu Ile Gly Met Lys
625                 630                 635                 640

Gly Glu Arg Arg Arg Gly Lys Gly His Asp Gly Leu Tyr Gln Gly Leu
                645                 650                 655

Ser Thr Ala Thr Lys Asp Thr Tyr Asp Ala Leu His Met Gln Ala Leu
            660                 665                 670

Pro Pro Arg Leu Glu Gly Gly Gly Glu Gly Arg Gly Ser Leu Leu Thr
        675                 680                 685

Cys Gly Asp Val Glu Glu Asn Pro Gly Pro Arg Met Pro Pro Pro Arg
    690                 695                 700

Leu Leu Phe Phe Leu Leu Phe Leu Thr Pro Met Glu Val Arg Pro Glu
705                 710                 715                 720

Glu Pro Leu Val Val Lys Val Glu Glu Gly Asp Asn Ala Val Leu Gln
                725                 730                 735

Cys Leu Lys Gly Thr Ser Asp Gly Pro Thr Gln Gln Leu Thr Trp Ser
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            740                 745                 750

Arg Glu Ser Pro Leu Lys Pro Phe Leu Lys Leu Ser Leu Gly Leu Pro
        755                 760                 765

Gly Leu Gly Ile His Met Arg Pro Leu Ala Ile Trp Leu Phe Ile Phe
    770                 775                 780

Asn Val Ser Gln Gln Met Gly Gly Phe Tyr Leu Cys Gln Pro Gly Pro
785                 790                 795                 800

Pro Ser Glu Lys Ala Trp Gln Pro Gly Trp Thr Val Asn Val Glu Gly
                805                 810                 815

Ser Gly Glu Leu Phe Arg Trp Asn Val Ser Asp Leu Gly Gly Leu Gly
            820                 825                 830

Cys Gly Leu Lys Asn Arg Ser Ser Glu Gly Pro Ser Ser Pro Ser Gly
        835                 840                 845

Lys Leu Met Ser Pro Lys Leu Tyr Val Trp Ala Lys Asp Arg Pro Glu
    850                 855                 860

Ile Trp Glu Gly Glu Pro Pro Cys Val Pro Pro Arg Asp Ser Leu Asn
865                 870                 875                 880

Gln Ser Leu Ser Gln Asp Leu Thr Met Ala Pro Gly Ser Thr Leu Trp
                885                 890                 895

Leu Ser Cys Gly Val Pro Pro Asp Ser Val Ser Arg Gly Pro Leu Ser
            900                 905                 910

Trp Thr His Val His Pro Lys Gly Pro Lys Ser Leu Leu Ser Leu Glu
        915                 920                 925

Leu Lys Asp Asp Arg Pro Ala Arg Asp Met Trp Val Met Glu Thr Gly
    930                 935                 940

Leu Leu Leu Pro Arg Ala Thr Ala Gln Asp Ala Gly Lys Tyr Tyr Cys
945                 950                 955                 960

His Arg Gly Asn Leu Thr Met Ser Phe His Leu Glu Ile Thr Ala Arg
                965                 970                 975

Pro Val Leu Trp His Trp Leu Leu Arg Thr Gly Gly Trp Lys Val Ser
            980                 985                 990

Ala Val Thr Leu Ala Tyr Leu Ile  Phe Cys Leu Cys Ser  Leu Val Gly
        995                 1000                1005

Ile Leu  His Leu Gln Arg Ala  Leu Val Leu Arg Arg  Lys Arg
    1010                1015                1020


<210> SEQ ID NO 100
<211> LENGTH: 653
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
      Synthetic polypeptide"

<400> SEQUENCE: 100

Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Lys Pro Gly Gly
1               5                   10                  15

Ser Leu Lys Leu Ser Cys Ala Ala Ser Gly Phe Lys Phe Ser Arg Tyr
            20                  25                  30

Ala Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
        35                  40                  45

Ala Thr Ile Ser Ser Gly Gly Ser Tyr Ile Tyr Tyr Pro Asp Ser Val
    50                  55                  60
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Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Val Lys Asn Thr Leu Tyr
65                  70                  75                  80

Leu Gln Met Ser Ser Leu Arg Ser Glu Asp Thr Ala Met Tyr Tyr Cys
                85                  90                  95

Ala Arg Arg Asp Tyr Asp Leu Asp Tyr Phe Asp Ser Trp Gly Gln Gly
            100                 105                 110

Thr Leu Val Thr Val Ser Ser Gly Ser Thr Ser Gly Gly Gly Ser Gly
        115                 120                 125

Gly Gly Ser Gly Gly Gly Gly Ser Gly Asp Ile Gln Met Thr Gln Ser
    130                 135                 140

Pro Ser Ser Leu Ser Ala Ser Val Gly Asp Arg Val Thr Ile Thr Cys
145                 150                 155                 160

Lys Ala Ser Arg Asp Ile Arg Ser Tyr Leu Thr Trp Tyr Gln Gln Lys
                165                 170                 175

Pro Gly Lys Ala Pro Lys Thr Leu Ile Tyr Tyr Ala Thr Ser Leu Ala
            180                 185                 190

Asp Gly Val Pro Ser Arg Phe Ser Gly Ser Gly Ser Gly Gln Asp Tyr
        195                 200                 205

Ser Leu Thr Ile Ser Ser Leu Glu Ser Asp Asp Thr Ala Thr Tyr Tyr
    210                 215                 220

Cys Leu Gln His Gly Glu Ser Pro Phe Thr Phe Gly Ser Gly Thr Lys
225                 230                 235                 240

Met Glu Ile Lys Arg Ala Glu Ser Lys Tyr Gly Pro Pro Cys Pro Pro
                245                 250                 255

Cys Pro Ala Pro Glu Phe Glu Gly Gly Pro Ser Val Phe Leu Phe Pro
            260                 265                 270

Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr
        275                 280                 285

Cys Val Val Val Asp Val Ser Gln Glu Asp Pro Glu Val Gln Phe Asn
    290                 295                 300

Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg
305                 310                 315                 320

Glu Glu Gln Phe Gln Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val
                325                 330                 335

Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser
            340                 345                 350

Asn Lys Gly Leu Pro Ser Ser Ile Glu Lys Thr Ile Ser Lys Ala Lys
        355                 360                 365

Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Gln Glu
    370                 375                 380

Glu Met Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe
385                 390                 395                 400

Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu
                405                 410                 415

Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe
            420                 425                 430

Phe Leu Tyr Ser Arg Leu Thr Val Asp Lys Ser Arg Trp Gln Glu Gly
        435                 440                 445

Asn Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr
    450                 455                 460
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Thr Gln Lys Ser Leu Ser Leu Ser Leu Gly Lys Met Ala Leu Ile Val
465                 470                 475                 480

Leu Gly Gly Val Ala Gly Leu Leu Leu Phe Ile Gly Leu Gly Ile Phe
                485                 490                 495

Phe Ala Val Ser Leu Ser Lys Met Leu Lys Lys Arg Ser Pro Leu Thr
            500                 505                 510

Thr Gly Val Tyr Val Lys Met Pro Pro Thr Glu Pro Glu Cys Glu Lys
        515                 520                 525

Gln Phe Gln Pro Tyr Phe Ile Pro Ile Asn Gly Gly Gly Arg Val Lys
    530                 535                 540

Phe Ser Arg Ser Ala Asp Ala Pro Ala Tyr Gln Gln Gly Gln Asn Gln
545                 550                 555                 560

Leu Tyr Asn Glu Leu Asn Leu Gly Arg Arg Glu Glu Tyr Asp Val Leu
                565                 570                 575

Asp Lys Arg Arg Gly Arg Asp Pro Glu Met Gly Gly Lys Pro Arg Arg
            580                 585                 590

Lys Asn Pro Gln Glu Gly Leu Tyr Asn Glu Leu Gln Lys Asp Lys Met
        595                 600                 605

Ala Glu Ala Tyr Ser Glu Ile Gly Met Lys Gly Glu Arg Arg Arg Gly
    610                 615                 620

Lys Gly His Asp Gly Leu Tyr Gln Gly Leu Ser Thr Ala Thr Lys Asp
625                 630                 635                 640

Thr Tyr Asp Ala Leu His Met Gln Ala Leu Pro Pro Arg
                645                 650


<210> SEQ ID NO 101
<211> LENGTH: 112
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
      Synthetic polypeptide"

<400> SEQUENCE: 101

Gly Pro Val Pro Pro Ser Thr Ala Leu Arg Tyr Leu Ile Glu Glu Leu
1               5                   10                  15

Val Asn Ile Thr Gln Asn Gln Lys Ala Pro Leu Cys Asn Gly Ser Met
            20                  25                  30

Val Trp Ser Ile Asn Leu Thr Ala Gly Met Tyr Cys Ala Ala Leu Glu
        35                  40                  45

Ser Leu Ile Asn Val Ser Gly Cys Ser Ala Ile Glu Lys Thr Gln Arg
    50                  55                  60

Met Leu Ser Gly Phe Cys Pro His Lys Val Ser Ala Gly Gln Phe Ser
65                  70                  75                  80

Ser Leu His Val Arg Asp Thr Lys Ile Glu Val Ala Gln Phe Val Lys
                85                  90                  95

Asp Leu Leu Leu His Leu Lys Lys Leu Phe Arg Glu Gly Arg Phe Asn
            100                 105                 110


<210> SEQ ID NO 102
<211> LENGTH: 245
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
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<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic polypeptide"

<400> SEQUENCE: 102

Asp Ile Gln Met Thr Gln Thr Thr Ser Ser Leu Ser Ala Ser Leu Gly
1 5 10 15

Asp Arg Val Thr Ile Ser Cys Arg Ala Ser Gln Asp Ile Ser Lys Tyr
20 25 30

Leu Asn Trp Tyr Gln Gln Lys Pro Asp Gly Thr Val Lys Leu Leu Ile
35 40 45

Tyr His Thr Ser Arg Leu His Ser Gly Val Pro Ser Arg Phe Ser Gly
50 55 60

Ser Gly Ser Gly Thr Asp Tyr Ser Leu Thr Ile Ser Asn Leu Glu Gln
65 70 75 80

Glu Asp Ile Ala Thr Tyr Phe Cys Gln Gln Gly Asn Thr Leu Pro Tyr
85 90 95

Thr Phe Gly Gly Gly Thr Lys Leu Glu Ile Thr Gly Ser Thr Ser Gly
100 105 110

Ser Gly Lys Pro Gly Ser Gly Glu Gly Ser Thr Lys Gly Glu Val Lys
115 120 125

Leu Gln Glu Ser Gly Pro Gly Leu Val Ala Pro Ser Gln Ser Leu Ser
130 135 140

Val Thr Cys Thr Val Ser Gly Val Ser Leu Pro Asp Tyr Gly Val Ser
145 150 155 160

Trp Ile Arg Gln Pro Pro Arg Lys Gly Leu Glu Trp Leu Gly Val Ile
165 170 175

Trp Gly Ser Glu Thr Thr Tyr Tyr Asn Ser Ala Leu Lys Ser Arg Leu
180 185 190

Thr Ile Ile Lys Asp Asn Ser Lys Ser Gln Val Phe Leu Lys Met Asn
195 200 205

Ser Leu Gln Thr Asp Asp Thr Ala Ile Tyr Tyr Cys Ala Lys His Tyr
210 215 220

Tyr Tyr Gly Gly Ser Tyr Ala Met Asp Tyr Trp Gly Gln Gly Thr Ser
225 230 235 240

Val Thr Val Ser Ser
245

<210> SEQ ID NO 103
<211> LENGTH: 98
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic polypeptide"

<400> SEQUENCE: 103

Asp Ile Gln Met Thr Gln Thr Thr Ser Ser Leu Ser Ala Ser Leu Gly
1 5 10 15

Asp Arg Val Thr Ile Ser Cys Arg Ala Ser Gln Asp Ile Ser Lys Tyr
20 25 30

Leu Asn Trp Tyr Gln Gln Lys Pro Asp Gly Thr Val Lys Leu Leu Ile
35 40 45

Tyr His Thr Ser Arg Leu His Ser Gly Val Pro Ser Arg Phe Ser Gly
50 55 60

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Ser Gly Ser Gly Thr Asp Tyr Ser Leu Thr Ile Ser Asn Leu Glu Gln
65 70 75 80

Glu Asp Ile Ala Thr Tyr Phe Cys Gln Gln Gly Asn Thr Leu Pro Tyr
85 90 95

Thr Phe

<210> SEQ ID NO 104
<211> LENGTH: 144
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic polypeptide"

<400> SEQUENCE: 104

Thr Lys Leu Glu Ile Thr Gly Ser Thr Ser Gly Ser Gly Lys Pro Gly
1 5 10 15

Ser Gly Glu Gly Ser Thr Lys Gly Glu Val Lys Leu Gln Glu Ser Gly
20 25 30

Pro Gly Leu Val Ala Pro Ser Gln Ser Leu Ser Val Thr Cys Thr Val
35 40 45

Ser Gly Val Ser Leu Pro Asp Tyr Gly Val Ser Trp Ile Arg Gln Pro
50 55 60

Pro Arg Lys Gly Leu Glu Trp Leu Gly Val Ile Trp Gly Ser Glu Thr
65 70 75 80

Thr Tyr Tyr Asn Ser Ala Leu Lys Ser Arg Leu Thr Ile Ile Lys Asp
85 90 95

Asn Ser Lys Ser Gln Val Phe Leu Lys Met Asn Ser Leu Gln Thr Asp
100 105 110

Asp Thr Ala Ile Tyr Tyr Cys Ala Lys His Tyr Tyr Tyr Gly Gly Ser
115 120 125

Tyr Ala Met Asp Tyr Trp Gly Gln Gly Thr Ser Val Thr Val Ser Ser
130 135 140

<210> SEQ ID NO 105
<211> LENGTH: 246
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic polypeptide"

<400> SEQUENCE: 105

Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Lys Pro Gly Gly
1 5 10 15

Ser Leu Lys Leu Ser Cys Ala Ala Ser Gly Phe Lys Phe Ser Arg Tyr
20 25 30

Ala Met Ser Trp Val Arg Gln Ala Pro Gly Lys Arg Leu Glu Trp Val
35 40 45

Ala Thr Ile Ser Ser Gly Gly Ser Tyr Ile Tyr Tyr Pro Asp Ser Val
50 55 60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Val Lys Asn Thr Leu Tyr
65 70 75 80

Leu Gln Met Ser Ser Leu Arg Ser Glu Asp Thr Ala Met Tyr Tyr Cys

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                85                  90                  95

Ala Arg Arg Asp Tyr Asp Leu Asp Tyr Phe Asp Ser Trp Gly Gln Gly
            100                 105                 110

Thr Leu Val Thr Val Ser Ser Gly Ser Thr Ser Gly Gly Gly Ser Gly
        115                 120                 125

Gly Gly Ser Gly Gly Gly Gly Ser Ser Asp Ile Gln Met Thr Gln Ser
    130                 135                 140

Pro Ser Ser Leu Ser Ala Ser Val Gly Asp Arg Val Thr Ile Thr Cys
145                 150                 155                 160

Lys Ala Ser Arg Asp Ile Arg Ser Tyr Leu Thr Trp Tyr Gln Gln Lys
                165                 170                 175

Pro Gly Lys Ala Pro Lys Thr Leu Ile Tyr Tyr Ala Thr Ser Leu Ala
            180                 185                 190

Asp Gly Val Pro Ser Arg Phe Ser Gly Ser Gly Ser Gly Gln Asp Tyr
        195                 200                 205

Ser Leu Thr Ile Ser Ser Leu Glu Ser Asp Asp Thr Ala Thr Tyr Tyr
    210                 215                 220

Cys Leu Gln His Gly Glu Ser Pro Phe Thr Phe Gly Ser Gly Thr Lys
225                 230                 235                 240

Leu Glu Ile Lys Arg Ala
                245


<210> SEQ ID NO 106
<211> LENGTH: 117
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
      Synthetic polypeptide"

<400> SEQUENCE: 106

Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Lys Pro Gly Gly
1               5                   10                  15

Ser Leu Lys Leu Ser Cys Ala Ala Ser Gly Phe Lys Phe Ser Arg Tyr
            20                  25                  30

Ala Met Ser Trp Val Arg Gln Ala Pro Gly Lys Arg Leu Glu Trp Val
        35                  40                  45

Ala Thr Ile Ser Ser Gly Gly Ser Tyr Ile Tyr Tyr Pro Asp Ser Val
    50                  55                  60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Val Lys Asn Thr Leu Tyr
65                  70                  75                  80

Leu Gln Met Ser Ser Leu Arg Ser Glu Asp Thr Ala Met Tyr Tyr Cys
                85                  90                  95

Ala Arg Arg Asp Tyr Asp Leu Asp Tyr Phe Asp Ser Trp Gly Gln Gly
            100                 105                 110

Thr Leu Val Thr Val
        115


<210> SEQ ID NO 107
<211> LENGTH: 109
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
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-continued

Synthetic polypeptide"

<400> SEQUENCE: 107

```
Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
1               5                   10                  15

Asp Arg Val Thr Ile Thr Cys Lys Ala Ser Arg Asp Ile Arg Ser Tyr
            20                  25                  30

Leu Thr Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Thr Leu Ile
        35                  40                  45

Tyr Tyr Ala Thr Ser Leu Ala Asp Gly Val Pro Ser Arg Phe Ser Gly
    50                  55                  60

Ser Gly Ser Gly Gln Asp Tyr Ser Leu Thr Ile Ser Ser Leu Glu Ser
65                  70                  75                  80

Asp Asp Thr Ala Thr Tyr Tyr Cys Leu Gln His Gly Glu Ser Pro Phe
                85                  90                  95

Thr Phe Gly Ser Gly Thr Lys Leu Glu Ile Lys Arg Ala
            100                 105
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<210> SEQ ID NO 108
<211> LENGTH: 246
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic polypeptide"

<400> SEQUENCE: 108

```
Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Lys Pro Gly Gly
1               5                   10                  15

Ser Leu Lys Leu Ser Cys Ala Ala Ser Gly Phe Lys Phe Ser Arg Tyr
            20                  25                  30

Ala Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
        35                  40                  45

Ala Thr Ile Ser Ser Gly Gly Ser Tyr Ile Tyr Tyr Pro Asp Ser Val
    50                  55                  60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Val Lys Asn Thr Leu Tyr
65                  70                  75                  80

Leu Gln Met Ser Ser Leu Arg Ser Glu Asp Thr Ala Met Tyr Tyr Cys
                85                  90                  95

Ala Arg Arg Asp Tyr Asp Leu Asp Tyr Phe Asp Ser Trp Gly Gln Gly
            100                 105                 110

Thr Leu Val Thr Val Ser Ser Gly Ser Thr Ser Gly Gly Gly Ser Gly
        115                 120                 125

Gly Gly Ser Gly Gly Gly Gly Ser Gly Asp Ile Gln Met Thr Gln Ser
    130                 135                 140

Pro Ser Ser Leu Ser Ala Ser Val Gly Asp Arg Val Thr Ile Thr Cys
145                 150                 155                 160

Lys Ala Ser Arg Asp Ile Arg Ser Tyr Leu Thr Trp Tyr Gln Gln Lys
                165                 170                 175

Pro Gly Lys Ala Pro Lys Thr Leu Ile Tyr Tyr Ala Thr Ser Leu Ala
            180                 185                 190

Asp Gly Val Pro Ser Arg Phe Ser Gly Ser Gly Ser Gly Gln Asp Tyr
        195                 200                 205
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```
Ser Leu Thr Ile Ser Ser Leu Glu Ser Asp Asp Thr Ala Thr Tyr Tyr
    210                 215                 220

Cys Leu Gln His Gly Glu Ser Pro Phe Thr Phe Gly Ser Gly Thr Lys
225                 230                 235                 240

Met Glu Ile Lys Arg Ala
                245


<210> SEQ ID NO 109
<211> LENGTH: 119
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
      Synthetic polypeptide"

<400> SEQUENCE: 109

Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Lys Pro Gly Gly
1               5                   10                  15

Ser Leu Lys Leu Ser Cys Ala Ala Ser Gly Phe Lys Phe Ser Arg Tyr
            20                  25                  30

Ala Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
        35                  40                  45

Ala Thr Ile Ser Ser Gly Gly Ser Tyr Ile Tyr Tyr Pro Asp Ser Val
    50                  55                  60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Val Lys Asn Thr Leu Tyr
65                  70                  75                  80

Leu Gln Met Ser Ser Leu Arg Ser Glu Asp Thr Ala Met Tyr Tyr Cys
                85                  90                  95

Ala Arg Arg Asp Tyr Asp Leu Asp Tyr Phe Asp Ser Trp Gly Gln Gly
            100                 105                 110

Thr Leu Val Thr Val Ser Ser
        115


<210> SEQ ID NO 110
<211> LENGTH: 109
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
      Synthetic polypeptide"

<400> SEQUENCE: 110

Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
1               5                   10                  15

Asp Arg Val Thr Ile Thr Cys Lys Ala Ser Arg Asp Ile Arg Ser Tyr
            20                  25                  30

Leu Thr Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Thr Leu Ile
        35                  40                  45

Tyr Tyr Ala Thr Ser Leu Ala Asp Gly Val Pro Ser Arg Phe Ser Gly
    50                  55                  60

Ser Gly Ser Gly Gln Asp Tyr Ser Leu Thr Ile Ser Ser Leu Glu Ser
65                  70                  75                  80

Asp Asp Thr Ala Thr Tyr Tyr Cys Leu Gln His Gly Glu Ser Pro Phe
                85                  90                  95

Thr Phe Gly Ser Gly Thr Lys Met Glu Ile Lys Arg Ala
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100 105

<210> SEQ ID NO 111
<211> LENGTH: 246
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> SEQUENCE: 111

Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
1 5 10 15

Asp Arg Val Thr Ile Thr Cys Lys Ala Ser Arg Asp Ile Arg Ser Tyr
20 25 30

Leu Thr Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Thr Leu Ile
35 40 45

Tyr Tyr Ala Thr Ser Leu Ala Asp Gly Val Pro Ser Arg Phe Ser Gly
50 55 60

Ser Gly Ser Gly Gln Asp Tyr Ser Leu Thr Ile Ser Ser Leu Glu Ser
65 70 75 80

Asp Asp Thr Ala Thr Tyr Tyr Cys Leu Gln His Gly Glu Ser Pro Phe
85 90 95

Thr Phe Gly Ser Gly Thr Lys Leu Glu Ile Lys Arg Ala Gly Ser Thr
100 105 110

Ser Gly Gly Gly Ser Gly Gly Gly Ser Gly Gly Gly Gly Ser Ser Glu
115 120 125

Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Lys Pro Gly Gly Ser
130 135 140

Leu Lys Leu Ser Cys Ala Ala Ser Gly Phe Lys Phe Ser Arg Tyr Ala
145 150 155 160

Met Ser Trp Val Arg Gln Ala Pro Gly Lys Arg Leu Glu Trp Val Ala
165 170 175

Thr Ile Ser Ser Gly Gly Ser Tyr Ile Tyr Tyr Pro Asp Ser Val Lys
180 185 190

Gly Arg Phe Thr Ile Ser Arg Asp Asn Val Lys Asn Thr Leu Tyr Leu
195 200 205

Gln Met Ser Ser Leu Arg Ser Glu Asp Thr Ala Met Tyr Tyr Cys Ala
210 215 220

Arg Arg Asp Tyr Asp Leu Asp Tyr Phe Asp Ser Trp Gly Gln Gly Thr
225 230 235 240

Leu Val Thr Val Ser Ser
245

<210> SEQ ID NO 112
<211> LENGTH: 109
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> SEQUENCE: 112

Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
1 5 10 15

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```
Asp Arg Val Thr Ile Thr Cys Lys Ala Ser Arg Asp Ile Arg Ser Tyr
            20                  25                  30

Leu Thr Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Thr Leu Ile
        35                  40                  45

Tyr Tyr Ala Thr Ser Leu Ala Asp Gly Val Pro Ser Arg Phe Ser Gly
    50                  55                  60

Ser Gly Ser Gly Gln Asp Tyr Ser Leu Thr Ile Ser Ser Leu Glu Ser
65                  70                  75                  80

Asp Asp Thr Ala Thr Tyr Tyr Cys Leu Gln His Gly Glu Ser Pro Phe
                85                  90                  95

Thr Phe Gly Ser Gly Thr Lys Met Glu Ile Lys Arg Ala
            100                 105


<210> SEQ ID NO 113
<211> LENGTH: 119
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
      Synthetic polypeptide"

<400> SEQUENCE: 113

Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Lys Pro Gly Gly
1               5                   10                  15

Ser Leu Lys Leu Ser Cys Ala Ala Ser Gly Phe Lys Phe Ser Arg Tyr
            20                  25                  30

Ala Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
        35                  40                  45

Ala Thr Ile Ser Ser Gly Gly Ser Tyr Ile Tyr Tyr Pro Asp Ser Val
    50                  55                  60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Val Lys Asn Thr Leu Tyr
65                  70                  75                  80

Leu Gln Met Ser Ser Leu Arg Ser Glu Asp Thr Ala Met Tyr Tyr Cys
                85                  90                  95

Ala Arg Arg Asp Tyr Asp Leu Asp Tyr Phe Asp Ser Trp Gly Gln Gly
            100                 105                 110

Thr Leu Val Thr Val Ser Ser
        115


<210> SEQ ID NO 114
<211> LENGTH: 1055
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
      Synthetic polypeptide"

<400> SEQUENCE: 114

Met Leu Leu Leu Val Thr Ser Leu Leu Leu Cys Glu Leu Pro His Pro
1               5                   10                  15

Ala Phe Leu Leu Ile Pro Asp Ile Gln Met Thr Gln Thr Thr Ser Ser
            20                  25                  30

Leu Ser Ala Ser Leu Gly Asp Arg Val Thr Ile Ser Cys Arg Ala Ser
        35                  40                  45
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Gln Asp Ile Ser Lys Tyr Leu Asn Trp Tyr Gln Gln Lys Pro Asp Gly
    50                  55                  60

Thr Val Lys Leu Leu Ile Tyr His Thr Ser Arg Leu His Ser Gly Val
65                  70                  75                  80

Pro Ser Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Tyr Ser Leu Thr
                85                  90                  95

Ile Ser Asn Leu Glu Gln Glu Asp Ile Ala Thr Tyr Phe Cys Gln Gln
            100                 105                 110

Gly Asn Thr Leu Pro Tyr Thr Phe Gly Gly Gly Thr Lys Leu Glu Ile
        115                 120                 125

Thr Gly Ser Thr Ser Gly Ser Gly Lys Pro Gly Ser Gly Glu Gly Ser
    130                 135                 140

Thr Lys Gly Glu Val Lys Leu Gln Glu Ser Gly Pro Gly Leu Val Ala
145                 150                 155                 160

Pro Ser Gln Ser Leu Ser Val Thr Cys Thr Val Ser Gly Val Ser Leu
                165                 170                 175

Pro Asp Tyr Gly Val Ser Trp Ile Arg Gln Pro Pro Arg Lys Gly Leu
            180                 185                 190

Glu Trp Leu Gly Val Ile Trp Gly Ser Glu Thr Thr Tyr Tyr Asn Ser
        195                 200                 205

Ala Leu Lys Ser Arg Leu Thr Ile Ile Lys Asp Asn Ser Lys Ser Gln
    210                 215                 220

Val Phe Leu Lys Met Asn Ser Leu Gln Thr Asp Asp Thr Ala Ile Tyr
225                 230                 235                 240

Tyr Cys Ala Lys His Tyr Tyr Tyr Gly Gly Ser Tyr Ala Met Asp Tyr
                245                 250                 255

Trp Gly Gln Gly Thr Ser Val Thr Val Ser Ser Glu Ser Lys Tyr Gly
            260                 265                 270

Pro Pro Cys Pro Pro Cys Pro Ala Pro Glu Phe Glu Gly Gly Pro Ser
        275                 280                 285

Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg
    290                 295                 300

Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser Gln Glu Asp Pro
305                 310                 315                 320

Glu Val Gln Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala
                325                 330                 335

Lys Thr Lys Pro Arg Glu Glu Gln Phe Gln Ser Thr Tyr Arg Val Val
            340                 345                 350

Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr
        355                 360                 365

Lys Cys Lys Val Ser Asn Lys Gly Leu Pro Ser Ser Ile Glu Lys Thr
    370                 375                 380

Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu
385                 390                 395                 400

Pro Pro Ser Gln Glu Glu Met Thr Lys Asn Gln Val Ser Leu Thr Cys
                405                 410                 415

Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser
            420                 425                 430

Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp
        435                 440                 445

Ser Asp Gly Ser Phe Phe Leu Tyr Ser Arg Leu Thr Val Asp Lys Ser
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    450                 455                 460

Arg Trp Gln Glu Gly Asn Val Phe Ser Cys Ser Val Met His Glu Ala
465                 470                 475                 480

Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Leu Gly Lys
                485                 490                 495

Met Ala Leu Ile Val Leu Gly Gly Val Ala Gly Leu Leu Leu Phe Ile
            500                 505                 510

Gly Leu Gly Ile Phe Phe Ala Val Ser Leu Ser Lys Met Leu Lys Lys
        515                 520                 525

Arg Ser Pro Leu Thr Thr Gly Val Tyr Val Lys Met Pro Pro Thr Glu
    530                 535                 540

Pro Glu Cys Glu Lys Gln Phe Gln Pro Tyr Phe Ile Pro Ile Asn Gly
545                 550                 555                 560

Gly Gly Arg Val Lys Phe Ser Arg Ser Ala Asp Ala Pro Ala Tyr Gln
                565                 570                 575

Gln Gly Gln Asn Gln Leu Tyr Asn Glu Leu Asn Leu Gly Arg Arg Glu
            580                 585                 590

Glu Tyr Asp Val Leu Asp Lys Arg Arg Gly Arg Asp Pro Glu Met Gly
        595                 600                 605

Gly Lys Pro Arg Arg Lys Asn Pro Gln Glu Gly Leu Tyr Asn Glu Leu
    610                 615                 620

Gln Lys Asp Lys Met Ala Glu Ala Tyr Ser Glu Ile Gly Met Lys Gly
625                 630                 635                 640

Glu Arg Arg Arg Gly Lys Gly His Asp Gly Leu Tyr Gln Gly Leu Ser
                645                 650                 655

Thr Ala Thr Lys Asp Thr Tyr Asp Ala Leu His Met Gln Ala Leu Pro
            660                 665                 670

Pro Arg Leu Glu Gly Gly Gly Glu Gly Arg Gly Ser Leu Leu Thr Cys
        675                 680                 685

Gly Asp Val Glu Glu Asn Pro Gly Pro Arg Met Leu Leu Leu Val Thr
    690                 695                 700

Ser Leu Leu Leu Cys Glu Leu Pro His Pro Ala Phe Leu Leu Ile Pro
705                 710                 715                 720

Arg Lys Val Cys Asn Gly Ile Gly Ile Gly Glu Phe Lys Asp Ser Leu
                725                 730                 735

Ser Ile Asn Ala Thr Asn Ile Lys His Phe Lys Asn Cys Thr Ser Ile
            740                 745                 750

Ser Gly Asp Leu His Ile Leu Pro Val Ala Phe Arg Gly Asp Ser Phe
        755                 760                 765

Thr His Thr Pro Pro Leu Asp Pro Gln Glu Leu Asp Ile Leu Lys Thr
    770                 775                 780

Val Lys Glu Ile Thr Gly Phe Leu Leu Ile Gln Ala Trp Pro Glu Asn
785                 790                 795                 800

Arg Thr Asp Leu His Ala Phe Glu Asn Leu Glu Ile Ile Arg Gly Arg
                805                 810                 815

Thr Lys Gln His Gly Gln Phe Ser Leu Ala Val Val Ser Leu Asn Ile
            820                 825                 830

Thr Ser Leu Gly Leu Arg Ser Leu Lys Glu Ile Ser Asp Gly Asp Val
        835                 840                 845

Ile Ile Ser Gly Asn Lys Asn Leu Cys Tyr Ala Asn Thr Ile Asn Trp
    850                 855                 860
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Lys Lys Leu Phe Gly Thr Ser Gly Gln Lys Thr Lys Ile Ile Ser Asn
865                 870                 875                 880

Arg Gly Glu Asn Ser Cys Lys Ala Thr Gly Gln Val Cys His Ala Leu
                885                 890                 895

Cys Ser Pro Glu Gly Cys Trp Gly Pro Glu Pro Arg Asp Cys Val Ser
            900                 905                 910

Cys Arg Asn Val Ser Arg Gly Arg Glu Cys Val Asp Lys Cys Asn Leu
        915                 920                 925

Leu Glu Gly Glu Pro Arg Glu Phe Val Glu Asn Ser Glu Cys Ile Gln
    930                 935                 940

Cys His Pro Glu Cys Leu Pro Gln Ala Met Asn Ile Thr Cys Thr Gly
945                 950                 955                 960

Arg Gly Pro Asp Asn Cys Ile Gln Cys Ala His Tyr Ile Asp Gly Pro
                965                 970                 975

His Cys Val Lys Thr Cys Pro Ala Gly Val Met Gly Glu Asn Asn Thr
            980                 985                 990

Leu Val Trp Lys Tyr Ala Asp Ala  Gly His Val Cys His  Leu Cys His
        995                 1000                1005

Pro Asn  Cys Thr Tyr Gly Cys  Thr Gly Pro Gly Leu  Glu Gly Cys
    1010                1015                1020

Pro Thr  Asn Gly Pro Lys Ile  Pro Ser Ile Ala Thr  Gly Met Val
    1025                1030                1035

Gly Ala  Leu Leu Leu Leu Leu  Val Val Ala Leu Gly  Ile Gly Leu
    1040                1045                1050

Phe Met
    1055


<210> SEQ ID NO 115
<211> LENGTH: 652
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
      Synthetic polypeptide"

<400> SEQUENCE: 115

Asp Ile Gln Met Thr Gln Thr Thr Ser Ser Leu Ser Ala Ser Leu Gly
1               5                   10                  15

Asp Arg Val Thr Ile Ser Cys Arg Ala Ser Gln Asp Ile Ser Lys Tyr
            20                  25                  30

Leu Asn Trp Tyr Gln Gln Lys Pro Asp Gly Thr Val Lys Leu Leu Ile
        35                  40                  45

Tyr His Thr Ser Arg Leu His Ser Gly Val Pro Ser Arg Phe Ser Gly
    50                  55                  60

Ser Gly Ser Gly Thr Asp Tyr Ser Leu Thr Ile Ser Asn Leu Glu Gln
65                  70                  75                  80

Glu Asp Ile Ala Thr Tyr Phe Cys Gln Gln Gly Asn Thr Leu Pro Tyr
                85                  90                  95

Thr Phe Gly Gly Gly Thr Lys Leu Glu Ile Thr Gly Ser Thr Ser Gly
            100                 105                 110

Ser Gly Lys Pro Gly Ser Gly Glu Gly Ser Thr Lys Gly Glu Val Lys
        115                 120                 125
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Leu Gln Glu Ser Gly Pro Gly Leu Val Ala Pro Ser Gln Ser Leu Ser
    130                 135                 140

Val Thr Cys Thr Val Ser Gly Val Ser Leu Pro Asp Tyr Gly Val Ser
145                 150                 155                 160

Trp Ile Arg Gln Pro Pro Arg Lys Gly Leu Glu Trp Leu Gly Val Ile
                165                 170                 175

Trp Gly Ser Glu Thr Thr Tyr Tyr Asn Ser Ala Leu Lys Ser Arg Leu
            180                 185                 190

Thr Ile Ile Lys Asp Asn Ser Lys Ser Gln Val Phe Leu Lys Met Asn
        195                 200                 205

Ser Leu Gln Thr Asp Asp Thr Ala Ile Tyr Tyr Cys Ala Lys His Tyr
    210                 215                 220

Tyr Tyr Gly Gly Ser Tyr Ala Met Asp Tyr Trp Gly Gln Gly Thr Ser
225                 230                 235                 240

Val Thr Val Ser Ser Glu Ser Lys Tyr Gly Pro Pro Cys Pro Pro Cys
                245                 250                 255

Pro Ala Pro Glu Phe Glu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro
            260                 265                 270

Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys
        275                 280                 285

Val Val Val Asp Val Ser Gln Glu Asp Pro Glu Val Gln Phe Asn Trp
    290                 295                 300

Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu
305                 310                 315                 320

Glu Gln Phe Gln Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu
                325                 330                 335

His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn
            340                 345                 350

Lys Gly Leu Pro Ser Ser Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly
        355                 360                 365

Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Gln Glu Glu
    370                 375                 380

Met Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr
385                 390                 395                 400

Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn
                405                 410                 415

Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe
            420                 425                 430

Leu Tyr Ser Arg Leu Thr Val Asp Lys Ser Arg Trp Gln Glu Gly Asn
        435                 440                 445

Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr
    450                 455                 460

Gln Lys Ser Leu Ser Leu Ser Leu Gly Lys Met Ala Leu Ile Val Leu
465                 470                 475                 480

Gly Gly Val Ala Gly Leu Leu Leu Phe Ile Gly Leu Gly Ile Phe Phe
                485                 490                 495

Ala Val Ser Leu Ser Lys Met Leu Lys Lys Arg Ser Pro Leu Thr Thr
            500                 505                 510

Gly Val Tyr Val Lys Met Pro Pro Thr Glu Pro Glu Cys Glu Lys Gln
        515                 520                 525

Phe Gln Pro Tyr Phe Ile Pro Ile Asn Gly Gly Gly Arg Val Lys Phe
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    530                 535                 540

Ser Arg Ser Ala Asp Ala Pro Ala Tyr Gln Gln Gly Gln Asn Gln Leu
545                 550                 555                 560

Tyr Asn Glu Leu Asn Leu Gly Arg Arg Glu Glu Tyr Asp Val Leu Asp
                565                 570                 575

Lys Arg Arg Gly Arg Asp Pro Glu Met Gly Gly Lys Pro Arg Arg Lys
            580                 585                 590

Asn Pro Gln Glu Gly Leu Tyr Asn Glu Leu Gln Lys Asp Lys Met Ala
        595                 600                 605

Glu Ala Tyr Ser Glu Ile Gly Met Lys Gly Glu Arg Arg Arg Gly Lys
    610                 615                 620

Gly His Asp Gly Leu Tyr Gln Gly Leu Ser Thr Ala Thr Lys Asp Thr
625                 630                 635                 640

Tyr Asp Ala Leu His Met Gln Ala Leu Pro Pro Arg
                645                 650


<210> SEQ ID NO 116
<211> LENGTH: 10
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
      Synthetic peptide"

<400> SEQUENCE: 116

Gly Gly Gly Ser Ser Gly Gly Gly Ser Gly
1               5                   10


<210> SEQ ID NO 117
<211> LENGTH: 12
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
      Synthetic peptide"

<400> SEQUENCE: 117

Glu Ser Lys Tyr Gly Pro Pro Cys Pro Pro Cys Pro
1               5                   10


<210> SEQ ID NO 118
<211> LENGTH: 12
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
      Synthetic peptide"

<400> SEQUENCE: 118

Glu Ser Lys Tyr Gly Pro Pro Cys Pro Ser Cys Pro
1               5                   10


<210> SEQ ID NO 119
<211> LENGTH: 22
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
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-continued

Synthetic peptide"

<400> SEQUENCE: 119

Glu Ser Lys Tyr Gly Pro Pro Cys Pro Pro Cys Pro Gly Gly Gly Ser
1 5 10 15

Ser Gly Gly Gly Ser Gly
20

<210> SEQ ID NO 120
<211> LENGTH: 39
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic polypeptide"

<400> SEQUENCE: 120

Ile Glu Val Met Tyr Pro Pro Pro Tyr Leu Asp Asn Glu Lys Ser Asn
1 5 10 15

Gly Thr Ile Ile His Val Lys Gly Lys His Leu Cys Pro Ser Pro Leu
20 25 30

Phe Pro Gly Pro Ser Lys Pro
35

<210> SEQ ID NO 121
<211> LENGTH: 48
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic polypeptide"

<400> SEQUENCE: 121

Ala Lys Pro Thr Thr Thr Pro Ala Pro Arg Pro Pro Thr Pro Ala Pro
1 5 10 15

Thr Ile Ala Ser Gln Pro Leu Ser Leu Arg Pro Glu Ala Cys Arg Pro
20 25 30

Ala Ala Gly Gly Ala Val His Thr Arg Gly Leu Asp Phe Ala Cys Asp
35 40 45

<210> SEQ ID NO 122
<211> LENGTH: 45
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic polypeptide"

<400> SEQUENCE: 122

Thr Thr Thr Pro Ala Pro Arg Pro Pro Thr Pro Ala Pro Thr Ile Ala
1 5 10 15

Ser Gln Pro Leu Ser Leu Arg Pro Glu Ala Cys Arg Pro Ala Ala Gly
20 25 30

Gly Ala Val His Thr Arg Gly Leu Asp Phe Ala Cys Asp
35 40 45

<210> SEQ ID NO 123
<211> LENGTH: 129

-continued

<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic polypeptide"

<400> SEQUENCE: 123

Glu Ser Lys Tyr Gly Pro Pro Cys Pro Pro Cys Pro Gly Gly Gly Ser
1 5 10 15

Ser Gly Gly Gly Ser Gly Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr
20 25 30

Leu Pro Pro Ser Gln Glu Glu Met Thr Lys Asn Gln Val Ser Leu Thr
35 40 45

Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu
50 55 60

Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu
65 70 75 80

Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Arg Leu Thr Val Asp Lys
85 90 95

Ser Arg Trp Gln Glu Gly Asn Val Phe Ser Cys Ser Val Met His Glu
100 105 110

Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Leu Gly
115 120 125

Lys

<210> SEQ ID NO 124
<211> LENGTH: 229
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic polypeptide"

<400> SEQUENCE: 124

Glu Ser Lys Tyr Gly Pro Pro Cys Pro Ser Cys Pro Ala Pro Glu Phe
1 5 10 15

Glu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr
20 25 30

Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val
35 40 45

Ser Gln Glu Asp Pro Glu Val Gln Phe Asn Trp Tyr Val Asp Gly Val
50 55 60

Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Phe Gln Ser
65 70 75 80

Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu
85 90 95

Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Gly Leu Pro Ser
100 105 110

Ser Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro
115 120 125

Gln Val Tyr Thr Leu Pro Pro Ser Gln Glu Glu Met Thr Lys Asn Gln
130 135 140

Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala
145 150 155 160

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Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr
                165                 170                 175

Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Arg Leu
            180                 185                 190

Thr Val Asp Lys Ser Arg Trp Gln Glu Gly Asn Val Phe Ser Cys Ser
        195                 200                 205

Val Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser
    210                 215                 220

Leu Ser Leu Gly Lys
225


<210> SEQ ID NO 125
<211> LENGTH: 229
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
      Synthetic polypeptide"

<400> SEQUENCE: 125

Glu Ser Lys Tyr Gly Pro Pro Cys Pro Pro Cys Pro Ala Pro Glu Phe
1               5                   10                  15

Glu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr
            20                  25                  30

Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val
        35                  40                  45

Ser Gln Glu Asp Pro Glu Val Gln Phe Asn Trp Tyr Val Asp Gly Val
    50                  55                  60

Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Phe Gln Ser
65                  70                  75                  80

Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu
                85                  90                  95

Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Gly Leu Pro Ser
            100                 105                 110

Ser Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro
        115                 120                 125

Gln Val Tyr Thr Leu Pro Pro Ser Gln Glu Glu Met Thr Lys Asn Gln
    130                 135                 140

Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala
145                 150                 155                 160

Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr
                165                 170                 175

Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Arg Leu
            180                 185                 190

Thr Val Asp Lys Ser Arg Trp Gln Glu Gly Asn Val Phe Ser Cys Ser
        195                 200                 205

Val Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser
    210                 215                 220

Leu Ser Leu Gly Lys
225


<210> SEQ ID NO 126
<211> LENGTH: 107
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<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic polypeptide"

<400> SEQUENCE: 126

Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Gln Glu
1 5 10 15

Glu Met Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe
20 25 30

Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu
35 40 45

Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe
50 55 60

Phe Leu Tyr Ser Arg Leu Thr Val Asp Lys Ser Arg Trp Gln Glu Gly
65 70 75 80

Asn Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr
85 90 95

Thr Gln Lys Ser Leu Ser Leu Ser Leu Gly Lys
100 105

<210> SEQ ID NO 127
<211> LENGTH: 4
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic peptide"

<400> SEQUENCE: 127

Gly Gly Gly Ser
1

<210> SEQ ID NO 128
<211> LENGTH: 21
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic peptide"

<400> SEQUENCE: 128

Leu Cys Tyr Leu Leu Asp Gly Ile Leu Phe Ile Tyr Gly Val Ile Leu
1 5 10 15

Thr Ala Leu Phe Leu
20

<210> SEQ ID NO 129
<211> LENGTH: 27
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 129

Phe Trp Val Leu Val Val Val Gly Gly Val Leu Ala Cys Tyr Ser Leu
1 5 10 15

Leu Val Thr Val Ala Phe Ile Ile Phe Trp Val
20 25

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<210> SEQ ID NO 130
<211> LENGTH: 28
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 130

Met Phe Trp Val Leu Val Val Val Gly Gly Val Leu Ala Cys Tyr Ser
1 5 10 15

Leu Leu Val Thr Val Ala Phe Ile Ile Phe Trp Val
20 25

<210> SEQ ID NO 131
<211> LENGTH: 22
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 131

Met Ala Leu Ile Val Leu Gly Gly Val Ala Gly Leu Leu Leu Phe Ile
1 5 10 15

Gly Leu Gly Ile Phe Phe
20

<210> SEQ ID NO 132
<211> LENGTH: 21
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 132

Ile Tyr Ile Trp Ala Pro Leu Ala Gly Thr Cys Gly Val Leu Leu Leu
1 5 10 15

Ser Leu Val Ile Thr
20

<210> SEQ ID NO 133
<211> LENGTH: 23
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 133

Ile Tyr Ile Trp Ala Pro Leu Ala Gly Thr Cys Gly Val Leu Leu Leu
1 5 10 15

Ser Leu Val Ile Thr Leu Tyr
20

<210> SEQ ID NO 134
<211> LENGTH: 24
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 134

Ile Tyr Ile Trp Ala Pro Leu Ala Gly Thr Cys Gly Val Leu Leu Leu
1 5 10 15

Ser Leu Val Ile Thr Leu Tyr Cys
20

<210> SEQ ID NO 135
<211> LENGTH: 27
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

-continued

<400> SEQUENCE: 135

Ile Ile Ser Phe Phe Leu Ala Leu Thr Ser Thr Ala Leu Leu Phe Leu
1 5 10 15

Leu Phe Phe Leu Thr Leu Arg Phe Ser Val Val
            20 25

<210> SEQ ID NO 136
<211> LENGTH: 21
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 136

Pro Phe Phe Phe Cys Cys Phe Ile Ala Val Ala Met Gly Ile Arg Phe
1 5 10 15

Ile Ile Met Val Ala
            20

<210> SEQ ID NO 137
<211> LENGTH: 112
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 137

Arg Val Lys Phe Ser Arg Ser Ala Asp Ala Pro Ala Tyr Gln Gln Gly
1 5 10 15

Gln Asn Gln Leu Tyr Asn Glu Leu Asn Leu Gly Arg Arg Glu Glu Tyr
            20 25 30

Asp Val Leu Asp Lys Arg Arg Gly Arg Asp Pro Glu Met Gly Gly Lys
        35 40 45

Pro Arg Arg Lys Asn Pro Gln Glu Gly Leu Tyr Asn Glu Leu Gln Lys
    50 55 60

Asp Lys Met Ala Glu Ala Tyr Ser Glu Ile Gly Met Lys Gly Glu Arg
65 70 75 80

Arg Arg Gly Lys Gly His Asp Gly Leu Tyr Gln Gly Leu Ser Thr Ala
                85 90 95

Thr Lys Asp Thr Tyr Asp Ala Leu His Met Gln Ala Leu Pro Pro Arg
            100 105 110

<210> SEQ ID NO 138
<211> LENGTH: 41
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 138

Arg Ser Lys Arg Ser Arg Leu Leu His Ser Asp Tyr Met Asn Met Thr
1 5 10 15

Pro Arg Arg Pro Gly Pro Thr Arg Lys His Tyr Gln Pro Tyr Ala Pro
            20 25 30

Pro Arg Asp Phe Ala Ala Tyr Arg Ser
        35 40

<210> SEQ ID NO 139
<211> LENGTH: 41
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 139

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```
Arg Ser Lys Arg Ser Arg Gly Gly His Ser Asp Tyr Met Asn Met Thr
1               5                   10                  15

Pro Arg Arg Pro Gly Pro Thr Arg Lys His Tyr Gln Pro Tyr Ala Pro
            20                  25                  30

Pro Arg Asp Phe Ala Ala Tyr Arg Ser
        35                  40


<210> SEQ ID NO 140
<211> LENGTH: 42
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 140

Lys Arg Gly Arg Lys Lys Leu Leu Tyr Ile Phe Lys Gln Pro Phe Met
1               5                   10                  15

Arg Pro Val Gln Thr Thr Gln Glu Glu Asp Gly Cys Ser Cys Arg Phe
            20                  25                  30

Pro Glu Glu Glu Glu Gly Gly Cys Glu Leu
        35                  40


<210> SEQ ID NO 141
<211> LENGTH: 42
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 141

Ala Leu Tyr Leu Leu Arg Arg Asp Gln Arg Leu Pro Pro Asp Ala His
1               5                   10                  15

Lys Pro Pro Gly Gly Gly Ser Phe Arg Thr Pro Ile Gln Glu Glu Gln
            20                  25                  30

Ala Asp Ala His Ser Thr Leu Ala Lys Ile
        35                  40


<210> SEQ ID NO 142
<211> LENGTH: 120
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 142

Trp Arg Arg Lys Arg Lys Glu Lys Gln Ser Glu Thr Ser Pro Lys Glu
1               5                   10                  15

Phe Leu Thr Ile Tyr Glu Asp Val Lys Asp Leu Lys Thr Arg Arg Asn
            20                  25                  30

His Glu Gln Glu Gln Thr Phe Pro Gly Gly Gly Ser Thr Ile Tyr Ser
        35                  40                  45

Met Ile Gln Ser Gln Ser Ser Ala Pro Thr Ser Gln Glu Pro Ala Tyr
    50                  55                  60

Thr Leu Tyr Ser Leu Ile Gln Pro Ser Arg Lys Ser Gly Ser Arg Lys
65                  70                  75                  80

Arg Asn His Ser Pro Ser Phe Asn Ser Thr Ile Tyr Glu Val Ile Gly
                85                  90                  95

Lys Ser Gln Pro Lys Ala Gln Asn Pro Ala Arg Leu Ser Arg Lys Glu
            100                 105                 110

Leu Glu Asn Phe Asp Val Tyr Ser
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```

-continued

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Leu Lys Leu Ser
20

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<400> SEQUENCE: 144

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<210> SEQ ID NO 145
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<400> SEQUENCE: 145

Arg Asp Tyr Asp Leu Asp Tyr Phe Asp Ser Trp Gly Gln Gly Thr Leu
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Val Thr Val

<210> SEQ ID NO 146
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<400> SEQUENCE: 146

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1 5 10 15

Ser Leu Lys Leu Ser Cys Ala Ala Ser Gly Phe Lys Phe Ser Arg Tyr
20 25 30

Ala Met Ser Trp Val Arg Gln Ala Pro Gly Lys Arg Leu Glu Trp Val
35 40 45

Ala Thr Ile Ser Ser Gly Gly Ser Tyr Ile Tyr Tyr Pro Asp Ser Val
50 55 60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Val Lys Asn Thr Leu Tyr
65 70 75 80

-continued

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Leu Gln Met Ser Ser Leu Arg Ser Glu Asp Thr Ala Met Tyr Tyr Cys
                85                  90                  95

Ala Arg Arg Asp Tyr Asp Leu Asp Tyr Phe Asp Ser Trp Gly Gln Gly
            100                 105                 110

Thr Leu Val Thr Val Ser Ser
        115
```

What is claimed is:

1. A nucleic acid encoding a chimeric antigen receptor (CAR) or polypeptide comprising a single chain variable fragment (scFv) targeted to CD6, a hinge region, a transmembrane domain, a CTLA4 signaling domain or a 41BB signaling domain, and a CD3 zeta signaling domain.

2. A nucleic acid encoding a chimeric antigen receptor (CAR) or polypeptide comprising a single chain variable fragment (scFv) targeted to CD19, a hinge region, a transmembrane domain, a CTLA4 signaling domain and a CD3 zeta signaling domain.

3. A nucleic acid encoding a chimeric antigen receptor (CAR) or polypeptide comprising an IL-13, a hinge region, a transmembrane domain, a CTLA4 signaling domain and a CD3 zeta signaling domain.

4. The nucleic acid of any one of claims **1**-**3**, wherein said transmembrane domain comprises a CD4 transmembrane domain or a variant thereof, a CD8 transmembrane domain or a variant thereof, a CD28 transmembrane domain or a variant thereof, or a CD3ζ transmembrane domain or a variant thereof.

5. The nucleic acid of claim **1**, wherein the CAR or polypeptide comprises or consists of an amino acid sequence at least 90, 95, 96, 97, 98, or 99% identical to any of SEQ ID Nos: 83-90 and 93-100.

6. The nucleic acid of claim **1**, wherein the CAR or polypeptide comprises or consists of an amino acid sequence of any of SEQ ID Nos: 83-90 and 93-100 with no more than 5 single amino acid substitutions.

7. The nucleic acid of claim **2**, wherein the CAR or polypeptide comprises or consists of an amino acid sequence at least 90, 95, 96, 97, 98, or 99% identical to any of SEQ ID Nos: 114-115.

8. The nucleic acid of claim **2**, wherein the CAR or polypeptide comprises or consists of an amino acid sequence of any of SEQ ID Nos: 114-115 with no more than 5 single amino acid substitutions.

9. The nucleic acid of claim **3**, wherein the CAR or polypeptide comprises or consists of an amino acid sequence at least 90, 95, 96, 97, 98, or 99% identical to any of SEQ ID Nos: 91-92.

10. The nucleic acid of claim **3**, wherein the CAR or polypeptide comprises or consists of an amino acid sequence of any of SEQ ID Nos: 91-92 with no more than 5 single amino acid substitutions.

11. The nucleic acid of claim **1**, wherein the scFv is as depicted in FIG. **1**-**5** or **17**A-**20**B.

12. The nucleic acid of claim **2**, wherein the scFv is as depicted in FIG. **21**A-**21**B.

13. The nucleic acid of claim **3**, wherein the IL-13 is as depicted in FIG. **16**A-**16**B.

14. The nucleic acid of claim **1** or **11**, wherein the scFv comprises any of SEQ ID NOs:105-113.

15. The nucleic acid of claim **2** or **12**, wherein the scFv comprises any of SEQ ID NOs:102-104.

16. The nucleic acid of claim **1**, wherein the IL-13 comprises SEQ ID NO: 101.

17. A vector comprising the nucleic acid of any one of claims **1**-**16**.

18. The vector of claim **17**, wherein said vector is a viral vector.

19. A population of T cells transduced by a vector comprising the nucleic acid of any one of claims **1**-**16** or expressing the CAR or polypeptide encoded by the nucleic acid of any one of claims **1**-**16**.

20. The population of T cells of claim **19**, wherein the T cells are regulatory T cells or effector T cells.

21. The population of T cells of claim **19**, wherein at least 70%, 80%, or 90% of the cells are selected from:

(a) $CD4^+$ $CD25^{high}$,
(b) $CD4^+$ $CD25^{high}$ $CD127^{low}$,
(c) $CD4^+$ $CD25^{high}$ $CD127^-$,
(d) $CD4^+$ $CD25^{high}$ $CD6^{low}$,
(e) $CD4^+$ $CD25^{high}$ $CD6^-$,
(f) $CD4^+$ $CD25^{high}$ $CD127^{low}$ $CD6^{low}$,
(g) $CD4^+$ $CD25^{high}$ $CD127^-$ $CD6^{low}$,
(h) $CD4^+$ $CD25^{high}$ $CD127^{low}$ $CD6^-$,
(i) $CD4^+$ $CD25^{high}$ $CD127^-$ $CD6^-$,
(j) $CD3^+$ $CD6^{low}$, or
(k) $CD3^+$ $CD6^-$.

22. A chimeric antigen receptor (CAR) or polypeptide comprising a single chain variable fragment (scFv) targeted to CD6, a hinge region, a transmembrane domain, a CTLA4 signaling domain or a 41BB signaling domain, and a CD3 zeta signaling domain.

23. A chimeric antigen receptor (CAR) or polypeptide comprising a single chain variable fragment (scFv) targeted to CD19, a hinge region, a transmembrane domain, a CTLA4 signaling domain, and a CD3 zeta signaling domain.

24. A chimeric antigen receptor (CAR) or polypeptide comprising an IL-13, a hinge region, a transmembrane domain, a CTLA4 signaling domain, and a CD3 zeta signaling domain.

25. The CAR or polypeptide of any one of claims **22**-**24**, wherein said transmembrane domain comprises a CD4 transmembrane domain or a variant thereof, a CD8 transmembrane domain or a variant thereof, a CD28 transmembrane domain or a variant thereof, or a CD3ζ transmembrane domain or a variant thereof.

26. The CAR or polypeptide of claim **22**, wherein the scFv is as depicted in FIG. **1**-**5** or **17**A-**20**B.

27. The CAR or polypeptide of claim **23**, wherein the scFv is as depicted in FIGS. **21**A-**21**B.

28. The CAR or polypeptide of claim **24**, wherein the IL-13 is as depicted in FIGS. **16**A-**16**B.

29. The CAR or polypeptide of claim **22** or **28**, wherein the scFv comprises any of SEQ ID NOs:105-113.

30. The CAR or polypeptide of claim **22** or **28**, wherein the scFv comprises SEQ ID NOs:105.

31. The CAR or polypeptide of claim **22** or **28**, wherein the scFv comprises SEQ ID NOs:106.

32. The CAR or polypeptide of claim **23** or **29**, wherein the scFv comprises any of SEQ ID NOs:102-104.

33. The CAR or polypeptide of claim **24** or **30**, wherein the IL-13 comprises SEQ ID NO: 101.

34. The CAR or polypeptide of claim **22**, wherein the CAR or polypeptide comprises or consists of an amino acid sequence at least 90, 95, 96, 97, 98, or 99% identical to any of SEQ ID Nos: 83-90 and 93-100.

35. The CAR or polypeptide of claim **22**, wherein the CAR or polypeptide comprises or consists of an amino acid sequence of any of SEQ ID Nos: 83-90 and 93-100 with no more than 5 single amino acid substitutions.

36. The CAR or polypeptide of claim **23**, wherein the CAR or polypeptide comprises or consists of an amino acid sequence at least 90, 95, 96, 97, 98, or 99% identical to any of SEQ ID Nos: 114-115.

37. The CAR or polypeptide of claim **23**, wherein the CAR or polypeptide comprises or consists of an amino acid sequence of any of SEQ ID Nos: 114-115 with no more than 5 single amino acid substitutions.

38. The CAR or polypeptide of claim **24**, wherein the CAR or polypeptide comprises or consists of an amino acid sequence at least 90, 95, 96, 97, 98, or 99% identical to any of SEQ ID Nos: 91-92.

39. The CAR or polypeptide of claim **24**, wherein the CAR or polypeptide comprises or consists of an amino acid sequence of any of SEQ ID Nos: 91-92 with no more than 5 single amino acid substitutions.

40. The CAR or polypeptide of any one of claims **22-24**, further comprising an intracellular T-cell signaling domain.

41. The CAR or polypeptide of claim **40**, wherein said intracellular T-cell signaling domain is a CD3ζ intracellular T-cell signaling domain.

42. A CAR or polypeptide encoded by the nucleic acid of any one of claims **1-16**.

43. A population of T cells comprising, or expressing, the CAR or polypeptide of any one of claims **22-42**.

44. The population of T cells of claim **43**, wherein said T cells are regulatory T cells or effector T cells.

45. The population of T cells of claim **43**, wherein at least 70%, 80%, or 90% of the cells selected from:

(a) $CD4^+$ $CD25^{high}$,

(b) $CD4^+$ $CD25^{high}$ $CD127^{low}$,

(c) $CD4^+$ $CD25^{high}$ $CD127^-$,

(d) $CD4^+$ $CD25^{high}$ $CD6^{low}$,

(e) $CD4^+$ $CD25^{high}$ $CD6^-$,

(f) $CD4^+$ $CD25^{high}$ $CD127^{low}$ $CD6^{low}$,

(g) $CD4^+$ $CD25^{high}$ $CD127^-$ $CD6^{low}$,

(h) $CD4^+$ $CD25^{high}$ $CD127^{low}$ $CD6^-$,

(i) $CD4^+$ $CD25^{high}$ $CD127^-$ $CD6^-$,

(j) $CD3^+$ $CD6^{low}$, or

(k) $CD3^+$ $CD6^-$.

46. The population of T cells of any one of claims **43-45**, wherein at least 70%, 80%, or 90% of cells are $CD6^{low}$ or $CD6^-$.

47. A composition comprising the population of T cells of any one of claims **19-21** or **43-46**.

48. A method of treating a cancer, the method comprising administering to a subject in need thereof a population of T cells harboring the nucleic acid of any one of claim **1-16**, the population of T cells of any one of claims **19-21** or **43-46**, or the composition of claim **47**.

49. The method of claim **48**, wherein the population of T cells are autologous human T cells or allogenic human T cells.

50. The method of claim **49**, wherein the cancer is a lymphoproliferative cancer.

51. The method of claim **49**, wherein the cancer comprises cells expressing CD6, CD19, or IL-13Rα2.

52. The method of claim **49**, wherein the cancer is a glioblastoma, primary brain tumors and gliomas (glioblastoma multiforme WHO Grade IV, anaplastic astrocytoma WHO Grade III, low-grade astrocytoma WHO Grade II, pilocytic astrocytoma WHO Grade I, other ungraded gliomas, oligodendroglioma, gliosarcoma, ganglioglioma, meningioma, ependymona), neuroectodermal tumors (medulloblastoma, neuroblastoma, ganglioneuroma, melanoma (metastatic), melanoma (primary), pheochromocytoma, Ewing's sarcoma, primitive neuroectodermal tumors, small cell lung carcinoma, Schwannoma), other brain tumors (epidermoid cysts, brain tumors of unknown pathology, pituitary gland of glioblastoma multiforme pt., metastatic tumors to brain of unknown tissue origin), melanoma, melanoma metastases, breast cancer, breast cancer metastases, kidney cancer, kidney cancer metastases, liver cancer, liver cancer metastases, lung cancer, lung cancer metastases, lymphoma, lymphoma metastases, ovarian cancer, ovarian cancer metastases, pancreatic cancer, pancreatic cancer metastases, prostate cancer, prostate cancer metastases, colorectal cancer, colorectal cancer metastases, combinations thereof.

53. A method of treating an autoimmune disease, the method comprising administering to a subject in need thereof a population of T cells harboring the nucleic acid of any one of claim **1-16**, the population of T cells of any one of claims **19-21** or **43-46**, or the composition of claim **47**.

54. The method of claim **53**, wherein the population of T cells are autologous human T cells or allogenic human T cells.

55. The method of claim **53**, wherein said autoimmune disease is Type I Diabetes or Graft-versus-Host Disease.

56. A method of killing, eliminating, or reducing cells expressing CD6, said method comprising administering to a subject in need thereof a population of T cells harboring the nucleic acid of any one of claim **1-16**, the population of T cells of any one of claims **19-21** or **43-46**, or the composition of claim **47**.

57. The method of claim **56**, wherein the population of T cells are autologous human T cells or allogenic human T cells.

58. The method of claim **56**, wherein the cells expressing CD6 are cancerous.

59. A method of killing, eliminating, or reducing cells expressing CD19, said method comprising administering to a subject in need thereof a population of T cells harboring the nucleic acid of any one of claim **1-16**, the population of T cells of any one of claims **19-21** or **43-46**, or the composition of claim **47**.

60. The method of claim **59**, wherein the population of T cells are autologous human T cells or allogenic human T cells.

61. The method of claim **59**, wherein the cells expressing CD19 are cancerous.

62. A method of killing, eliminating, or reducing cells expressing an IL-13R (e.g. IL-13Rα2), said method comprising administering to a subject in need thereof a population of T cells harboring the nucleic acid of any one of claim **1-16**, the population of T cells of any one of claims **19-21** or **43-46**, or the composition of claim **47**.

63. The method of claim **62**, wherein the population of T cells are autologous human T cells or allogenic human T cells.

64. The method of claim **62**, wherein the cells expressing an IL-13R are cancerous.

65. The method of any of claims **48-64**, wherein the population of T cells or composition are administered in single or repeat dosing

66. The method of **65**, wherein as effective amount is administered or at least one symptom is reduced, ameliorated, or relieved.

* * * * *